CANNABINOID RECEPTOR LIGANDS

CROSS REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of U.S. Serial No. 10/072,354, filed February 6, 2002, which claims priority to U.S. Provisional Application 60/267,375, filed February 8, 2001.

BACKGROUND OF THE INVENTION

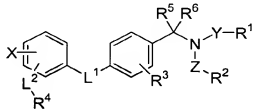
This invention relates to cannabinoid receptor ligands and, more particularly, to compounds that bind to cannabinoid (CB_2) receptors. Compounds according to the present invention generally exhibit anti-inflammatory and immunomodulatory activity and are useful in treating conditions characterized by inflammation and immunomodulatory irregularities. Examples of conditions which may be treated include, but are not limited to, rheumatoid arthritis, asthma, allergy, psoriasis, Crohn's disease, systemic lupus erythematosus, multiple sclerosis, diabetes, cancer, glaucoma, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, and nephritis. The invention also relates to pharmaceutical compositions containing said compounds.

Cannabinoid receptors belong to the superfamily of G-protein coupled receptors. They are classified into the predominantly neuronal CB1 receptors and the predominantly peripheral CB2 receptors. While the effects of CB1 receptors are principally associated with the central nervous system, CB2 receptors are believed to have peripheral effects related to bronchial constriction, immunomodulation and inflammation. As such, a selective CB2 receptor binding agent is expected to have therapeutic utility in the control of diseases associated with inflammation, immunomodulation and bronchial constriction such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, inflammatory disorders of the lungs and gastrointestinal tract, and respiratory tract disorders such as reversible airway obstruction, chronic asthma and bronchitis (see, e.g., R.G. Pertwee, Curr. Med. Chem. 6(8), (1999), 635).

Various compounds have reportedly been developed which interact with CB_2 receptors and/or which have, *inter alia*, anti-inflammatory activity associated with cannabinoid receptors. See, e.g., U.S. Pat. Nos. 5,338,753, 5,462,960, 5,532,237, 5,925,768, 5,948,777, 5,990,170, 6,013,648 and 6,017,919.

SUMMARY OF THE INVENTION

This invention relates to compounds of formula I:



or a pharmaceutically acceptable salt or solvate thereof; wherein:

R^1 is selected from the group consisting of H, alkyl, haloC_1-C_6 alkyl, cycloalkyl, cycloalkylNH-, arylalkyl, heterocycloalkyl, heteroaryl, -N(R^2)$_2$, -N(R^2)aryl, unsubstituted aryl and aryl substituted with one to three X, wherein each R^2 can be the same or different and is independently selected when there are more than one R^2 present;

R^2 is selected from the group consisting of H and C_1-C_6 alkyl;

R^3 is 1-3 substituents selected from the group consisting of H, C_1-C_6 alkyl, Cl, F, CF_3, OCF_2H, OCF_3, OH and C_1-C_6 alkoxy, wherein R^3 can be the same or different and is independently selected when there are more than one R^3 present;

R^4 is selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, alkenyl, aryl, benzyl, heteroaryl, heterocycloalkyl, arylNH-, heteroarylNH-, cycloalkylNH-, N(R^2)$_2$, or N(R^2)aryl, said alkyl, alkoxy, cycloalkyl, alkenyl, phenyl, pyridine-N-oxide and heteroaryl optionally substituted with one to three X, wherein X can be the same or different and is independently selected when there are more than one X present;

R^5 is H or C_1-C_6 alkyl;

R^6 is H or C_1-C_6 alkyl; or

R^5 and R^6 taken together with the carbon atom to which they are attached form a carbonyl group;

L^1 is  , $-C(R^2)_2-$, $-C(O)-$, $-CHOR^2-$, $-C{=}NOR^5-$, $-SO_2-$, $-SO-$, $-S-$, $-O-$, $-N(R^2)-$, $-C(O)NR^2-$, $-N(R^2)C(O)-$, $-CHCF_2-$ or $-CF_2-$;

L^2 is a covalent bond, C_1-C_6 alkylene, $-C(R^2)_2-$,  , $-CHOR^2-$, $-C(R^2)OH$, $-C{=}NOR^5-$, $-SO_2-$, $-N(R^2)SO_2-$, $-SO-$, $-S-$, $-O-$, $-SO_2N(R^2)-$, $-N(R^2)_2-$, $-C(O)N(R^2)-$ or $-N(R^2)C(O)-$;

X is selected from the group consisting of H, halogen, CF_3, CN, OCF_2H, OCF_2CF_3, OCF_3, OR^2, C_1-C_6 alkyl, cycloalkyl, cycloalkoxy, C_1-C_6 alkoxy, alkoxyC_1-C_6 alkoxy, O-cycloalkyl, cycloalkylamino, cycloalkylalkoxy, heteroalkyl, $-OSO_2R^2$, $-COOR^2$, $-CON(R^2)_2$, $N(R^2)_2$, and NR^2aryl, wherein X can be the same or different, and is independently selected when there are more than one X present;

Y is a covalent bond, $-CH_2-$, $-SO_2-$, or $-C(O)-$;

Z is a covalent bond, $-CH_2-$, $-SO_2-$ or $-C(O)-$; or

Y, R^1, Z and R^2 can be taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl; with the following provisos:

L^2 and R^4, when taken together, cannot have two heteroatoms covalenty bonded together;

when R^2 is H, Z cannot be $-S(O)-$, $-SO_2-$, or $-C(O)-$; and

when Y is a covalent bond, R^1 cannot form a N-N bond with the nitrogen atom.

Cannabinoid receptor ligands according to the present invention have anti-inflammatory activity and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) or

bronchitis. It is contemplated that one or more compounds of this invention can be useful in treating more than one of the diseases listed.

Additionally, one or more compounds of the present invention can be co-administered or used in combination with one or more disease-modifying antirheumatic drugs (DMARDS) such as methotrexate, azathioprine leflunomide, penicillamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. One or more compounds of the invention can also be co-administered with or used in combination with one or more NSAIDS such as piroxicam, naproxen, indomethacin, ibuprofen and the like; one or more COX-2 selective inhibitors such as Vioxx® and Celebrex®; one or more COX-1 inhibitors such as Feldene; immunosuppressives such as steroids, cyclosporine, Tacrolimus, rapamycin, muromonab-CD3 (OKT3), Basiliximab and the like; biological response modifiers (BRMs) such as Enbrel, Remicade, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, TACE inhibitors, chemokine receptor antagonists, Thalidomide and/or other small molecule inhibitors of pro-inflammatory cytokine production. One or more compounds of this invention can also be co-administered with or used in combination with one or more H1 antagonists such as Claritin, Clarinex, Zyrtec, Allegra, Benadryl, and other H1 antagonists. Other drugs that the compounds of the invention can be co-administered or used in combination with include Anaprox, Arava, Arthrotec, Azulfidine, Aspirin, Cataflam, Celestone Soluspan, Clinoril, Cortone Acetate, Cuprimine, Daypro, Decadron, Depen, Depo-Medrol, Disalcid, Dolobid, Naprosyn, Gengraf, Hydrocortone, Imuran, Indocin, Lodine, Motrin, Myochrysine, Nalfon, Naprelan, Neoral, Orudis, Oruvail, Pediapred, Plaquenil, Prelone, Relafen, Solu-Medrol, Tolectin, Trilisate and/or Volataren. These include any formulations of the above-named drugs.

For the treatment of multiple sclerosis, one or more compounds of the invention can be co-administered or used in combination with Avonex, Betaseron, Rebif and/or Copaxone. These include any formulations of the above-named drugs.

For the treatment of psoriasis, one or more compounds of the invention can be co-administered or used in combination with steroids, methotrexate, cyclosporin, Xanelin, Amivere, Vitamin D analogs, topical retinoids, anti-TNF-α compounds and/or

other drugs indicated for this condition. These include any formulations of the above-named drugs.

For the treatment of asthma, one or more compounds of the invention can be co-administered or used in combination with Singulair, Accolate, Albuterol, and/or other drugs indicated for this disease. These include any formulations of the above-named drugs.

For the treatment of inflammatory bowel disease or Crohn's disease, one or more compounds of the invention can be co-administered or used in combination with sulfasalazine, budesonide, mesalamine and/or other drugs indicated for these diseases. These include any formulations of the above-named drugs.

In another aspect, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of formula I in one or more pharmaceutically acceptable carriers.

DETAILED DESCRIPTION

Unless otherwise defined, the following definitions shall apply throughout the specification and claims.

When any variable (e.g., R^2) occurs more than one time in any constituent, its definition in each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain 1 to about 6 carbon atoms in the chain. Branched alkyl means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Preferred alkyl groups in the present invention are lower alkyl groups. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, trifluoromethyl and cyclopropylmethyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising 2 to 15

carbon atoms in the chain. Preferred alkenyl groups have 2 to 2 carbon atoms in the chain; and more preferably 2 to 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means 2 to 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, and n-pentenyl.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Haloalkyl" or "halogenated alkyl" means alkyl having one or more halo atom substituents. Non-limiting examples include $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2-CH_2Cl$, $-CH_2-CHCl_2$, and $-CHCl-CH_2Cl$.

"Heteroalkyl" means straight or branched alkyl chain as defined above comprising 1 or more heteroatoms, which can be the same or different, and are independently selected from the group consisting of N, O and S.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, phenylethyl and naphthalenylmethyl. The aralkyl is linked to an adjacent moiety through the alkyl.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylamino, arylamino, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, aralkyloxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio and cycloalkyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic fused ring system comprising 3 to 10 ring carbon atoms, preferably 3 to 7 ring carbon atoms, more preferably 3 to 6 ring carbon atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are

as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornenyl, adamantyl and the like.

"Cycloheteroalkyl" means a non-aromatic mono- or multicyclic fused ring system comprising 3 to 10 ring carbon atoms, preferably 3 to 7 ring carbon atoms, more preferably 3 to 6 ring carbon atoms, wherein the cycloheteroaryl has 1 or 2 heteroatoms independently selected from O, S or N, said heteroatom(s) interrupting a carbocyclic ring structure provided that the rings do not contain adjacent oxygen and/or sulfur atoms.. The cycloheteroalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "solvate" as used herein means an aggregate that consists of a solute ion or molecule with one or more solvent molecules, for example, a hydrate containing such ions.

As used herein, the terms "composition" and "formulation are intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combination of the specified ingredients. "Heterocycloalkyl" means cycloalkyl containing one or more heteroatoms.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising from 6 to 14 carbon atoms. Non-limiting examples include phenyl, naphthyl, indenyl, tetrahydronaphthyl and indanyl. The aryl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above.

"Heteroaryl" means a single ring or benzofused heteroaromatic group of 5 to 10 atoms comprised of 1 to 9 carbon atoms and 1 or more heteroatoms independently selected from the group consisting of N, O and S. N-oxides of the ring nitrogens are also included, as well as compounds wherein a ring nitrogen is substituted by a C_1-C_6 alkyl group to form a quaternary amine. Examples of single-ring heteroaryl groups are pyridyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazinyl, pyrimidyl, pyridazinyl and

triazolyl. Examples of benzofused heteroaryl groups are indolyl, quinolyl, isoquinolyl, phthalazinyl, benzothienyl (i.e., thionaphthenyl), benzimidazolyl, benzofuranyl, benzoxazolyl and benzofurazanyl. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl.

"Alkoxy" means an alkyl radical attached by an oxygen, i.e., alkoxy groups having 1 to 9 carbon atoms.

"Oxime" means a CH(:NOH) radical containing moiety.

The term "prodrug," as used herein, represents compounds which are rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

Linker groups such as L^1, L^2, Y and Z are divalent.

In a preferred group of compounds of formula I,

L^1 is $-SO_2-$, $-CH_2-$, $-CHCH_3-$, $-C(O)-$, $-C{=}NOR^5-$, $-C(CH_3)_2-$, $-CHOH-$, $-O-$, $-S-$ or $-S(O)-$;

L^2 is $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$,  , $-NH-$, $-O-$, , $-NHSO_2-$, $-NHC(O)-$, or ;

R^1 is H, $-CH_3NH_2$, $-CH_2CF_3$, $-NHC_3H_7$, $-NHC_2H_6$, $-NHC_4H_9$, C_1-C_6 alkyl, $-CF_3$, $-CH(CH_2)_2$, thiophenyl, morpholinyl, cyclopropyl, benzyl, naphthyl, $-C(CH_3)_3$, NHphenyl, 3,5-difluorophenyl, phenyl, N-cyclopentyl or $N(CH_3)_2$;

R^2 is H or CH_3;

R^3 is OH;

R^4 is furanyl, pyridyl, pyrimidyl, thiophenyl, quinolyl, t-butoxy, alkoxyl, cyclohexyl, phenyl, tolyl, C_3H_7, pyrimdyl, methoxyphenyl, morpholinylphenyl or CH_3; with the proviso that when R^4 is t-butoxy, L^2 must be -C(O)-, $-CH_2-$, $-CHCH_3-$, $-C(CH_3)_2-$or $-C(=CH_2)-$, all of the above optionally substituted with one to three X, wherein X can be the same or different and are independently selected when the are more than one X present;

R^5 and R^6 are independently H or CH_3;

Y is a covalent bond, $-SO_2-$ or -C(O)-;

Z is a covalent bond; or

R^1, Y, R^2 and Z taken together with the nitrogen atom form a morpholinyl group.

In a more preferred embodiment of the invention,

X is halogen, OH, or cyclopropyl;

R^3 is OH;

R^5 and R^6 are independently H or CH_3;

X is H, halogen, CF_3, OCH_3, OH, OCF_3, OCF_2H, CH_3 or C_1-C_6 cycloalkyl;

Y is a covalent bond;

Z is $-SO_2-$ or -C(O)-;

L^1 is $-SO_2-$ or $-CH_2-$;

L^2 is $-SO_2-$;

R^1 is CH_3 or CF_3; and

R^4 is phenyl, pyrimidyl or pyridyl, said phenyl, pyrimidyl or pyridyl groups optionally substituted with one to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, OH, CF_3 and halogen, wherein said substituents can be the same or different and are independently selected when there are more than one subsituent.

More preferably, the phenyl is substituted with OCH_3 or halogen selected from fluorine and chlorine.

Compounds of the invention may have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers are

contemplated as being part of this invention. The invention includes (+)- and (-)-isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optionally pure or optically enriched starting materials or by separating isomers of a compound of formula I. Those skilled in the art will appreciate that for some compounds of formula I, one isomer may show greater pharmacological activity that other isomers.

Compounds of formula I can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

Compounds of the invention with a basic group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

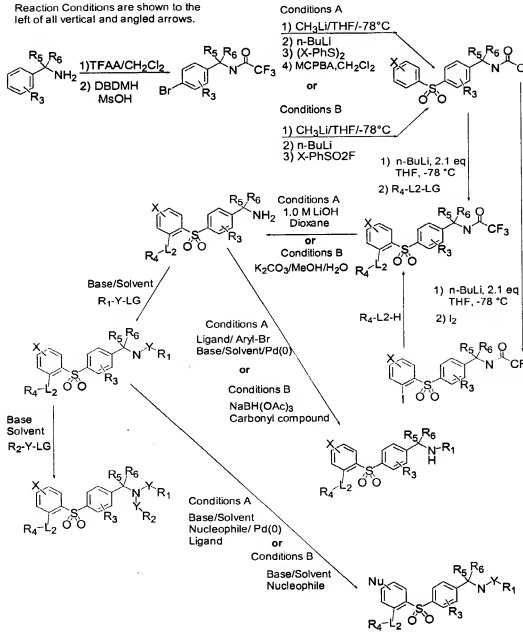
Certain compounds of the invention are acidic (e.g., compounds where R^2 is a hydrogen covalently bonded to N). Acidic compounds according to the present invention can form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, magnesium, zinc, lithium, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine, piperazines and other amines.

Compounds of the present invention are generally prepared by processes known in the art, for example by the processes described below.

The following abbreviations are used in the procedures and schemes: aqueous (aq), anhydrous (anhyd), n-butyllithium (n-BuLi), dibromodimethylhydantoin (DBDMH), diisopropylethylamine (DIPEA), diethyl ether (Et_2O), dimethylacetamide (DMA),

dimethyl sulfoxide (DMSO), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethanol (EtOH), ethyl acetate (EtOAc), 2-propanol (IPA), leaving group (LG), lithium hexamethyldisilazide (LHMDS), meta-chloroperoxybenzoic acid (MCPBA), methanesulfonic acid (MsOH), methanesulfonyl chloride (MsCl), N-iodosuccinamide (NIS), preparative thin layer chromatography on Merck- silica plates (PTLC), phenyl (Ph), pyridinium chlorochromate (PCC), pyridine (Py), trifluoroacetic anhydride (TFAA), triflic anhydride (Tf_2O), tetrahydrofuran (THF), silica gel chromatography (sgc), thin layer chromatography (TLC), room temperature (rt), hours (h), minutes (min), molar (M), pounds per square inch (psi), and saturated aqueous sodium chloride solution (brine).

General Scheme I
Preparation of Aryl-Bis-Sulfone Compounds



Description of Reactions-General Scheme I

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and reacted with a benzyl amine at room temperature for 1-5 hr. MsOH (2 eq) is added followed by DBDMH and the reaction mixture is stirred

overnight at room temperature and subjected to aqueous work up. The crude product is recrystallized from a mixture of Et_2O and hexanes or purified via chromatography.

In step 2, the product of step 1 is dissolved in THF, cooled in a dry ice/IPA bath and treated with methyllithium then n-BuLi. The resulting dianion may be trapped with a sulfonyl fluoride or a disulfide. If a disulfide is the trapping agent, the resulting product is oxidized with MCPBA in CH_2Cl_2 at room temperature for 1-6 h. The product may be purified via chromatography or crystallization.

In step 3, the product of step 2 is dissolved in THF and treated with n-BuLi at –78 °C to form a dianion that is trapped with a suitable electrophile.

Alternatively, in step 3 the product of step 2 is dissolved in THF treated with n-BuLi at –78 °C to form a dianion which is trapped with iodine to provide the iodo substituted product. The product may be purified via sgc or crystallization. The iodo product can be converted to a similar product by nucleophilic aromatic substitution with a variety of nucleophiles, including amines, alcohols, and thiols.

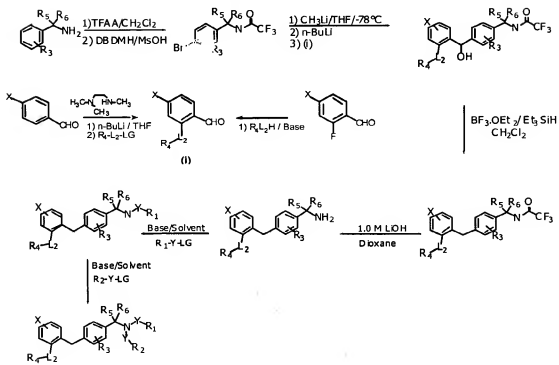
In step 4, the product of step 3 is dissolved in a suitable solvent such as dioxane, ethanol, methanol or THF and an alkali metal hydroxide or carbonate such as lithium hydroxide or potassium carbonate is added either as an aqueous solution or as a solid. The reaction mixture is stirred at room temperature for 0.5-24 h. The product may be purified via sgc or crystallization.

In step 5, a combination of the product of step 4 and a tertiary amine base was dissolved in a suitable solvent such as CH_2Cl_2 or dioxane, at room temperature, cooled, and a suitable electrophile is added. The reaction mixture is stirred between -78 °C and 100 °C for 0.5 to 48 h. The product may be purified via sgc or crystallization.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as THF or CH_2Cl_2 and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0 °C and 100°C for 0.5 to 48 h. The product may be purified via sgc or crystallization.

General Scheme II

Preparation of Methylene Linked Compounds



Description of reactions-General Scheme II

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and treated with a benzyl amine at ambient temperature, then stirred for 1-5 h. Methanesulfonic acid (2 eq) is added followed by dibromodimethylhydantoin and the reaction mixture is stirred overnight at rt and subjected to aqueous work up. The product may be purified by chromatography or crystallization.

In step 2, the product of step 1 is dissolved in THF, cooled in a dry ice/acetone bath (-78°C) and treated with methyllithium, then n-BuLi. The dianion is then treated with a THF solution containing the aldehyde (i). The resulting mixture is warmed to rt and stirred for 10 h. The product is purified by chromatography.

In step 3, the alcohol product from step 2 is dissolved in methylene chloride and treated with ten fold excess of triethylsilane followed by a slight excess of boron trifluoride etherate. The resulting mixture is stirred at room temperature for 4h, and purified by chromatography.

In step 4, the product of step 3 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is

added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt for 0.5-24 h.

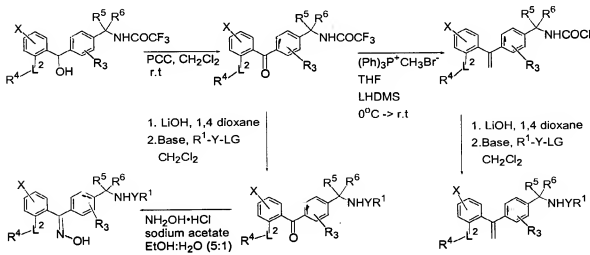
In step 5, the product of step 4 is dissolved in a mixture of a suitable inert solvent such as CH_2Cl_2 or dioxane and a tertiary amine base, and a suitable electrophile is added. The reaction mixture is stirred between -78 °C and 100 °C for 0.5 to 48 h.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as THF or CH_2Cl_2 and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0 °C and 100 °C for 0.5 to 48 h.

The aldehyde (i) used in step 2 was prepared by one of the following two procedures; 1) Regioselective ortho lithiation of a 4-substituted benzaldehyde, and quenching with a substituted phenyl disulfide followed by oxidation with metachloroperoxybenzoic acid to the sulfone. 2) Base promoted displacement of fluoride from an ortho-fluorobenzaldehyde by a thiophenol, phenol, or aniline.

General Scheme III

Preparation of Ketone and Olefin Linked Compounds



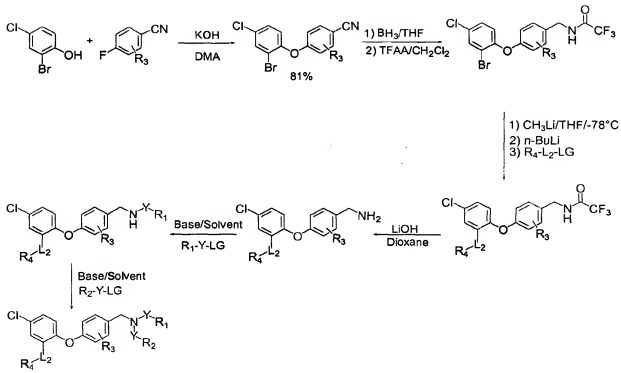
Description of reactions-General Scheme III

In step 1 the secondary alcohol, the product of Step 2 in Scheme II is oxidized with PCC, in a suitable inert solvent such as CH_2Cl_2, to the carbonyl by stirring at rt for 18 h. In step 2, the ketone is treated with the ylide obtained by base treatment of dried methyltriphenylphosphonium bromide, providing the exo methylene product. In

step 3 the trifluoroacetamide group can be hydrolyzed with base and reacted with a variety of acylating, sulfonylating, alkylating and other electrophilic reagents.

The ketone product can be treated with hydroxylamine hydrochloride in pyridine and heated at 80°C for 24 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. Upon workup and purification, the oxime is obtained.

General Scheme IV
Preparation of Oxygen Linked Compounds



Description of reactions-General Scheme IV

In step 1, 2-bromo-4-chlorophenol and a 4-fluorobenzonitrile are dissolved in a polar aprotic solvent such as DMA in the presence of a suitable base such as potassium hydroxide. The reaction mixture is heated for 0.5-7 days. Preferred temperatures are greater than 60 °C. The reaction mixture is diluted with a suitable extraction solvent such as diethyl ether and washed with water. The solvents are removed and the product is purified via sgc.

In step 2, the product of step 1 is dissolved in a solution of diborane in THF. The reaction is stirred at reflux for 1-24 h then quenched with water and partitioned between EtOAc and aq NaOH. The solvents are evaporated and the product is purified by formation of the HCl salt in diethyl ether.

In step 3, the product of step 2 is suspended in CH_2Cl_2 and a suitable base such as triethylamine is added. The reaction mixture is cooled, and TFAA is added. The reaction mixture is stirred from 0.5 to 8 h, then subjected to aqueous workup. The crude product is purified by sgc.

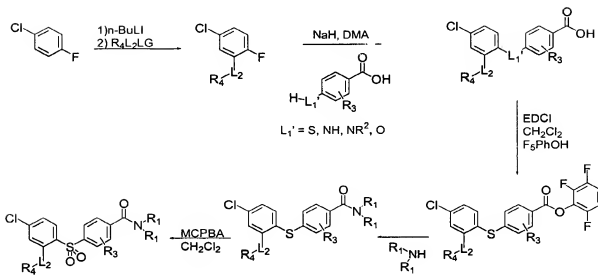
In step 4, the product of step 3 is dissolved in THF and treated with methyl lithium, then n-BuLi at –78 °C to form a dianion that is trapped with a suitable electrophile. The reaction mixture is quenched with a suitable proton source such as aq NH_4Cl or phosphate buffer then extracted with EtOAc. The product may be purified via sgc or crystallization.

In step 5, the product of step 4 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt for 0.5-24 h.

In step 6, the product of step 5 is dissolved in a mixture of a suitable inert solvent such as CH_2Cl_2 or dioxane and a tertiary amine base, and a suitable electrophile is added. The reaction mixture is stirred between -78°C and 100 °C for 0.5 to 48 h.

In step 7, the product of step 6 is dissolved in a suitable inert solvent such as THF or CH_2Cl_2 and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0°C and 100°C for 0.5 to 48 h.

General Scheme V
Preparation of Sulfer linked Compounds



Description of Reactions-General Scheme V

In step 1, 1-chloro-4-fluorobenzene is dissolved in anhyd THF and treated with n-BuLi at –78 °C to form an anion that is trapped with a suitable electrophile. The product may be purified via sgc or crystallization.

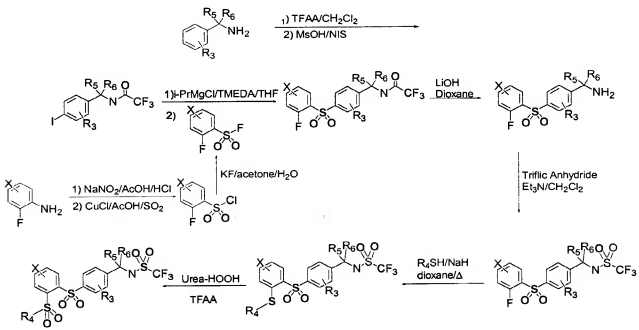
In step 2, the product of step 1 is dissolved in a suitable polar solvent such as acetonitrile or DMA. A benzoic acid containing a nucleophilic moiety such as an OH, NHR, or SH is added, and two or more equivalents of a suitable base such as potassium hydroxide or sodium hydride is added. The reaction mixture may be stirred for 1-24 h at temperatures ranging between 0°C and 150°C. The reaction mixture is partitioned between water and a suitable solvent such as EtOAc. The product may be purified via sgc or crystallization.

In step 3, the product of step 2 is dissolved in CH_2Cl_2. Pentafluorophenol and EDCI are added. The reaction mixture is stirred at rt for 0.5-24 h then partitioned between water and CH_2Cl_2. The solvents are evaporated. The product may be purified via sgc or crystallization.

In step 4, the product of step 3 is dissolved in a suitable solvent such as CH_2Cl_2. An amine base such as DIPEA or triethylamine is added, followed by a primary or secondary amine. The reaction mixture may be stirred for 1-24 h at rt. The reaction mixture is then subjected to aqueous workup and isolation and the product is purified via sgc.

In step 5, if the nucleophilic moiety in step 2 contains oxidizable functionality, the product of step 4 is dissolved in a suitable solvent such as CH_2Cl_2 and MCPBA is added. The reaction mixture may be stirred for 0.5-48 h then partitioned between a suitable solvent such as CH_2Cl_2 or EtOAc and an aqueous base such as Na_2CO_3. The solvent is evaporated and the product is purified via sgc.

General Scheme VI
Addition Elimination Chemistry



Description of Reactions-General Scheme VI

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and reacted with a benzyl amine at rt for 1-5 h. Methanesulfonic acid (2 eq) is added followed by N-iodosuccinamide. The reaction mixture is stirred overnight at rt, then subjected to aqueous work up. The crude product is recrystallized from isopropanol and water.

In step 2, CuCl is dissolved in glacial acetic acid. The flask is cooled to 0 °C and SO_2 gas is bubbled in with stirring for 40 min. In a separate flask 2-fluoro-4-chloroaniline is dissolved in glacial acetic acid and concentrated HCl. The resulting

solution is cooled to 0 °C and treated with an aqueous solution of $NaNO_2$. The reaction mixture is stirred for 30 min at 0 °C and the contents are added to the flask containing the SO_2 solution causing vigorous gas evolution. The reaction is then allowed to warm to rt. The product is isolated by pouring the reaction mixture onto chipped ice, then filtering the resulting solid.

In step 3, the product of step 2 is dissolved in acetone. An aqueous solution of KF (2 eq) is added and the reaction mixture is stirred for 12-24 h at rt. The reaction mixture is extracted with a suitable solvent such as CH_2Cl_2 or Et_2O and the solvent is evaporated to afford the product.

In step 4, the product of step 1 is dissolved in THF and TMEDA is added. The flask is placed under N_2 blanket, and cooled to 0 °C. A solution of isopropyl magnesium chloride in THF is added and the reaction mixture is stirred for 1-4 h. The resulting solution is added to a flask containing the product of step 3 that was cooled with an ice-water bath. The reaction mixture is stirred for 1-3 h. The reaction is quenched with aqueous NH_4Cl and extracted with EtOAc. After evaporation of the solvent, the crude product is purified via sgc.

In step 5, the product of step 4 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt for 0.5-24 h. The product may be purified via sgc or crystallization.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as CH_2Cl_2 or acetonitrile and a tertiary amine base, and a triflic anhydride is added. The reaction mixture is stirred between -78°C and rt for 0.5 to 48 h. The product may be purified via sgc or crystallization.

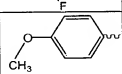
In step 7, the product of step 6 is dissolved in a suitable inert solvent such as dioxane and a thiol is added. A base such as sodium hydride, sodium hydroxide, or NaHMDS is added and the reaction mixture is stirred at a suitable temperature between 50 °C and 100 °C for 4-24 h. The reaction mixture is quenched with water and extracted with a suitable solvent. The solvents are evaporated and the crude product is purified via sgc.

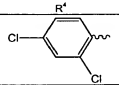
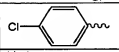
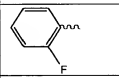
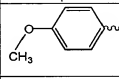
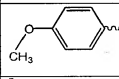
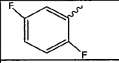
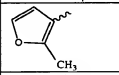
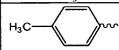
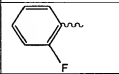
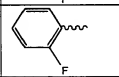
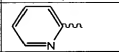
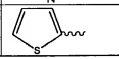
In step 8, the product of step 7 is dissolved in a suitable inert solvent such as CH_2Cl_2. Na_2HPO_4 and urea hydrogen peroxide complex is added, followed by TFAA.

The reaction mixture is refluxed for 4-16 h, then partitioned between water and CH_2Cl_2. The solvents are evaporated and the crude product is purified via sgc.

Those skilled in the art will appreciate that similar reactions to those described in the above schemes may be carried out on other compounds of formula I as long as substituents present would not be susceptible to the reaction conditions described. Starting materials for the above processes are either commercially available, known in the art, or prepared by procedures well known in the art. Exemplary compounds of formula 1 are set forth below in Table I. CB means covalent bond.

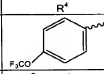
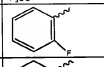
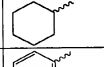
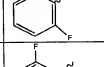
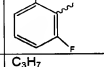
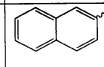
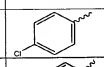
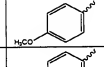
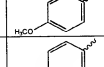
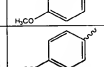
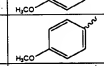
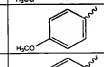
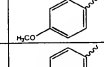
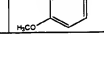
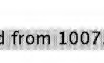
TABLE I

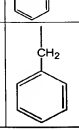
	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
A 412 702	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
B 225 336	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
C 414 093	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_2H	SO_2	CB
D 416 580	CH_3	H	H	t-butoxy	H	CH_3	SO_2	CO	OCH_3	SO_2	CB
E 425 084	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
F 406 921	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
G 425 800	CH_3	H	H		H	CH_3	SO_2	SO_2	CH_3	SO_2	CB
H 457 497	CF_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB

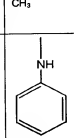
	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
I 405 560	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
J 377 315	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_3	SO	CB
K 420 752	CH_3	H	H	t-butoxy	H	CH_3	SO_2	C=O	OCF_2H	SO_2	CB
L 356 036	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
M 351 036	CH_3	H	H		H	H	SO_2	SO_2	OCH_3	SO_2	CB
N 364 967	CH_3	H	H		H	H	CH_2	SO_2	OCH_3	SO_2	CB
O 414 513	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
P 356 963	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
Q 425 159	CH_3	H	H		H	CH_3	SO_2	SO_2	CH_3	SO_2	CB
R 425 742	CF_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
S 414 319	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
T 397 385	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
U 406 786	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
V 466 042	CF_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
W 414 428	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
X 443 902	CF_3	H	H		CH_3	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
Y 226 592	C_4H_9	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
Z 406 919	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
AA 362 059	CH_3	H	H	C_3H_7	H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
AB 425 741	CH_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AC 428 016	CH_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AE 428 017	CF_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AF 361 884	CH_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AG 466 724	CF_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AH 468 221	CF_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AI 354 270	CH_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
AK 383 624	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
AM 414 513	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AO 397 385	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AQ 406 920	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AR 479 748	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AS 390 364	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AT 442 333	$N(CH_3)_2$	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AU 356 674	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AV 356 035	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AW 382 716	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AX 387 876	CH_3	H	H	C_3H_7	H	CH_3	SO_2	SO_2	Cl	SO_2	CB
AY 418 169	CF_3	H	H		CH_3	CH_3	SO_2	SO_2	Cl	O ‖ C	CB
AZ 425 054	CF_3	H	H		CH_3	CH_3	SO_2	SO_2	Cl	SO_2	CB
BA 414 568	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_3	SO_2	CB
BB 414 386	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
BC 414 555	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_3	SO_2	CB
BD 483 018	CF_3	H	H		H	CH_3	SO_2	SO_2	OCF_3	SO_2	CB
BG 406 921	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
BH 412 473	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BJ 442 465	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
BN 354 990	CF_3	H	H	C_3H_7	H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BO 354 288	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BP 354 332	NHC_3H_7	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BR 351 121	CF_3	H	H		CH_3	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BS 351 674	CH_3	H	H		CH_3	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
BT 352 468	CH_3	CH_3	H		CH_3	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
BU 351 036	CH_3	H	H		H	H	SO_2	SO_2	OCH_3	SO_2	CB
BV 351 073	CH_3	CH_3	H		H	H	SO_2	SO_2	OCH_3	SO_2	CB
BW 226 387	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
BX 351 034	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
BY 351 056	CH_3	CH_3	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
BZ 425 801	CF_3	H	H		H	CH_3	SO_2	SO_2	CH_3	SO_2	CB
CA 425 [illegible]	CF_3	H	H		H	CH_3	SO_2	SO_2	CH_3	SO_2	CB
CB 442 107	CH_3	H	H		H	CH_3	SO_2	SO_2	CH_3	SO_2	CB
CC 356 091	CF_3	H	H	C_3H_7	H	CH_3	SO_2	SO_2	Cl	C=O	CB
CD 357 520	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
CE 425 199	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
CF 405 616	$-CH(CH_3)_2$	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CG 355 365	NH_2	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CH 351 995	C_4H_9	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CI 354 330	$-CHCF_3$	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CJ 352 005		H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CK 352 001		H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CL 352 006		H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB
CM 352 004		H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
CN 225 335	CH_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CO 226 590		H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CP 353 873	C_3H_7	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CQ 226 591		H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CR 226 599		H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CS 414 517	CH_3	H	H		H	CH_3	SO_2	SO_2	Cl	C=O	CB
CT 354 332	$NH\text{-}(CH_2)_2\text{-}CH_3$	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CU 352 638		H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB
CV 416 699	CF_3	H	H		H	CH_3	SO_2	C=O	OH	C=O	CB
CW 356 923	CH_3	H	H		H	CH_3	SO_2	SO_2	OH	SO_2	CB
CX 412 851	CH_3	H	H		H	CH_3	SO_2	SO_2	OH	SO_2	CB
CZ 355 842	CF_3	H	H		H	CH_3	SO_2	SO_2	OCF_2H	C=O	CB
DA 356 924	CH_3	H	H		H	CH_3	SO_2	SO_2	OCF_2H	SO_2	CB
DC 425 179	CF_3	H	H		H	CH_3	SO_2	C=O	OCH_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
DD 416 579	CF_3	H	H		H	CH_3	SO_2	C=O	OCH_3	C=O	CB
DE 425 174		H	H		H	CH_3	SO_2	C=O	OCH_3	C=O	CB
DF 413 958	CH_3	H	H		H	CH_3	SO_2	C=O	Cl	SO_2	CB
DG 446 123	CF_3	H	H		H	CH_3	SO_2	C=O	Cl	SO_2	CB
DH 412 854	CH_3	H	H		H	CH_3	SO_2	CH_2	Cl	SO_2	CB
DI 413 395	CH_3	H	H		H	CH_3	SO_2	C=O	Cl	SO_2	CB
DJ 414 379	CH_3	H	H		H	CH_3	SO_2	CH_2	Cl	SO_2	CB
DK 414 389	CH_3	H	H		H	CH_3	SO_2	C=O	Cl	SO_2	CB
DL 415 209	CH_3	H	H		H	CH_3	SO_2	$C=CH_2$	Cl	SO_2	CB
DM 416 498	CF_3	H	H		H	CH_3	SO_2		Cl	C=O	CB
DN 405 613	CF_3	H	H		H	CH_3	SO_2	C=O	Cl	C=O	CB
DP 418 083	CF_3	CH_3	H		H	CH_3	SO_2	$C=CH_2$	Cl	C=O	CB
DQ 419 092	CH_3	H	H		CH_3	CH_3	SO_2	C=O	Cl	SO_2	CB
DR 413 578	CH_3	H	H		H	CH_3	SO_2	NH	Cl	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
DS 414 703	CF_3	H	H		H	CH_3	SO_2	O	Cl	C=O	CB
DU 353 361	CH_3	H	H		H	CH_3	CH_2	SO_2	OCH_3	SO_2	CB
DV 414 324	CH_3	H	H		H	CH_3	CH_2	SO_2	Cl	SO_2	CB
DW 457 497	CF_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
DX 457 663	CH_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
DY 477 128	CF_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
DZ 477 129	CH_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
EA 470 688	CF_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
EC 466 325	CH_3	H	H		H	CH_3	CH_2	SO_2	CF_3	SO_2	CB
ED 416 721	CF_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	C=O	CB
EE 416 834	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EG 466 752	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EH 442 994	CF_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EI 468 252	CF_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
EJ 468 880	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EK 447 774	CF_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EL 364 967	CH_3	H	H		H	H	CH_2	SO_2	OCH_3	SO_2	CB
EN 442 993	CF_3	H	H		CH_3	CH_3	CH_2	SO_2	OCF_3	C=O	CB
EP 428 781	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
EU 417 265	CH_3	H	H		H	CH_3	C=O	SO_2	OCF_3	SO_2	CB
EV 353 393	CF_3	H	H		H	CH_3	C=O	SO_2	OCH_3	SO_2	CB
EW 425 736	CF_3	H	H		H	CH_3	C=O	O	H	C=O	CB
EX 226 359	CF_3	H	H		H	CH_3	C=O	O	H	C=O	CB
EY 434 537	CF_3	H	H		H	CH_3	C=O	O	Cl	C=O	CB
EZ 417 265	CH_3	H	H		H	CH_3	C=O	SO_2	OCF_3	C=O	CB
FA 351 597	CF_3	H	H		H	CH_3	C=O	$NHSO_2$	H	C=O	CB
FB 351 600	CF_3	H	H		H	CH_3	C=O	NHCO	H	C=O	CB
FC 417 266	CF_3	H	H		H	CH_3	$C=CH_2$	SO_2	OCF_3	C=O	CB
FD 418 027	CH_3	H	H		H	CH_3	$C=CH_2$	SO_2	OCF_3	SO_2	CB

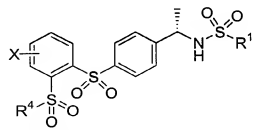
	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
FE 421 309	CF_3	H	H		H	CH_3	C=O	SO_2	OCF_3	SO_2	CB
FF 441 847	CH_3	H	H		H	CH_3	C=NO H	SO_2	OCF_3	SO_2	CB
FG 415 462	CH_3	H	H		H	CH_3	$C(CH_3)_2$	SO_2	Cl	SO_2	CB
FH 360 186	CF_3	H	H		H	H	C=O	SO_2	OCH_3	C=O	CB
FI 443 908	CH_3	H	H		H	H	O	SO_2	Cl	SO_2	CB
FJ 483 359	*R^1, Y, Z and R^2 combine to form morpholinyl	*	H		-	O ‖	S	SO_2	Cl	*	*
FK 483 774	H	CH_3	H		-	O ‖	S=O	SO_2	Cl	CB	CB
FL 483 776	H	CH_3	H		-	O ‖	SO_2	SO_2	Cl	CB	CB
FM 483 778	*R^1, Y, Z and R^2 combine to form morpholinyl	*	H		-	O ‖	SO_2	SO_2	Cl	*	*
FN 484 873	CH_3	CH_3	H		-	O ‖	S	SO_2	Cl	CB	CB
FO 484 874	H	H	H		-	O ‖	S	SO_2	Cl	CB	CB
FP 484 875	CH_3	CH_3	H		-	O ‖	SO_2	SO_2	Cl	CB	CB
FQ 484 878	H	H	H		-	O ‖	SO_2	SO_2	Cl	CB	CB
FR 413 596	CH_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
FS 412 570	CH_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB

	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
FT 414 048	CH_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
FU 412 850	CF_3	H	H		H	CH_3	SO_2	SO_2	H	C=O	CB
FV 416 711	CH_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
FW 417 314	CH_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
FX 355 185	CF_3	H	H		H	CH_3	SO_2	SO_2	H	C=O	CB
FY 442 680	CF_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
FZ 413 597	CF_3	H	H		H	CH_3	SO_2	SO_2	H	SO_2	CB
GA 446 122	CH_3	H	H		H	CH_3	CH_2	SO_2	OCF_3	C=O	CB
GD 445 579		H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
GF 468 098	NHC_2H_6	H	H		H	CH_3	CH_2	SO_2	OCF_3	SO_2	CB
GG 486 885	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
GH 487 886	CF_3	H	H		H	CH_3	SO_2	SO_2	CF_3	SO_2	CB
GI 487 185	CF_3	H	H		H	CH_3	SO_2	SO_2	Cl	SO_2	CB
GJ 484 872	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	SO_2	CB

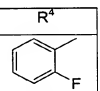
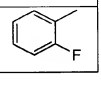
	R^1	R^2	R^3	R^4	R^5	R^6	L^1	L^2	X	Y	Z
GK 491 471	CF_3	H	H		H	CH_3	SO_2	C=O	OCH_3	SO_2	CB
GL 491 673	CF_3	H	H		H	CH_3	SO_2	SO_2	OH	SO_2	CB
GM 495 923	CF_3	H	H		H	CH_3	SO_2	SO_2	$OCH(CH_3)_2$	SO_2	CB
GN 494 867	CF_3	H	H		H	CH_3	SO_2	SO_2		SO_2	CB
GO 355 145	CF_3	H	H		H	CH_3	SO_2	SO_2	OCH_3	C=O	CB

CB is a covalent bond
- means that the substituent is not present

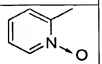
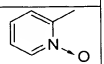
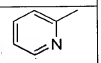
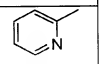
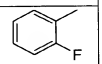
In a preferred embodiment, there are disclosed compounds of the formula



or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or of said prodrug; wherein X, R^1 and R^4 are as shown in the table below:

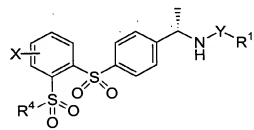
Example	X	R^1	R^4
A	OCH_3	CH_3	
C	OCF_2H	CH_3	

Example	X	R^1	R^4
G	CH_3	CH_3	
L	Cl	CH_3	
R	CF_3	CF_3	
S	Cl	CF_3	
AB	CF_3	CH_3	
AT	Cl	$N(CH_3)_2$	
BA	OCF_3	CH_3	
BD	OCF_3	CF_3	
BZ	CH_3	CF_3	
CD	Cl	CH_3	
FS	H	CH_3	
FY	H	CF_3	

Example	X	R^1	R^4
GG	Cl	CF_3	
GH	CF_3	CF_3	
XXIX		CF_3	
XXX		CF_3	
XXXI		CF_3	
XXXII	CN	CF_3	
XXXIII	NH_2	CF_3	
XXXIV		CF_3	
XXXVI	Cl	CF_3	
XXXVII		CF_3	
XXXVIII	CN	CF_3	
XXXIX	$CONH_2$	CF_3	

Example	X	R^1	R^4
XXXX	OCH_3	CF_3	
XXXXI	OH	CF_3	
XXXXII		CF_3	
XXXXIII		CF_3	
XXXXIV		CF_3	
XXXXV		CF_3	
LV	OCH_3	CF_3	
LVI		CH_3	

In another preferred embodiment, there are disclosed compounds of the formula



or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or of said prodrug; wherein X, Y-R^1 and R^4 are as shown in the table below:

Example	X	Y-R^1	R^4
XXXXVI			
XXXXVII			
XXXXVIII			
XXXXIX			
VI	OCH_3		
VII	OCH_3		
VIII	OCH_3		

Compound A SCH 412702: ^1H NMR (300 MHz, $CDCl_3$) 1.54 (d, J = 6.9Hz 3H), 2.67 (s, 3H), 4.72 (q, J = 5Hz 1H), 4.86 (br. d, J = 5Hz,1H, NH), 7.08-8.42 (m, 11H).

Compound C SCH 414093: ^1H NMR (400 MHz, $CDCl_3$) 1.51 (d, J = 7.2Hz 3H), 2.67 (s, 3H), 4.702 (q, J = 6.8Hz 1H), 5.05 (br. d, J = 6.4Hz,1H, NH), 6.71 (t, J = 71.6 Hz, CF2H) 7.07-8.47 (m, 11H).

Compound G Sch 425800: ^1H NMR (300 MHz, $CDCl_3$) 8.43-8.41 (m, 1H), 8.36 (d, 8Hz, 1H), 8.28-8.22 (m, 1H), 7.96-7.92 (m, 2H), 7.69-7.60 (m, 2H), 7.52-7.47 (m, 2H), 7.43-7.37 (m, 1H), 7.13-7.06 (m, 1H), 4.76-4.70 (m, 2H), 2.68 (s, 3H), 2.59 (s, 3H), 1.41 (d, 7 Hz, 3H).

Compound L Sch 356036: ^1H NMR (300 MHz, $CDCl_3$) 8.61-5.97 (m, 2H), 8.40 (d, 8 Hz, 1H), 8.24-8.21 (m, 1H), 7.96 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.70-7.63 (m, 1H),

7.52 (d, 8 Hz, 2H), 7.46-7.40 (m, 1H), 7.18-7.12 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.56 (d, 7Hz, 3H).

Compound R Sch 425742: ^{1}H NMR (300 MHz, $CDCl_3$) 8.89-8.87 (m, 1H), 8.58 (d, 8Hz, 1H), 8.32-8.25 (m, 1H), 8.15-8.11 (m, 1H), 8.03-7.98 (m, 2H), 7.71-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 5.62 (d, 8 Hz, 1H), 4.80-4.80 (m, 1H), 1.63 (d, 7 Hz, 3H).

Compound S Sch 414319: ^{1}H NMR (300 MHz, $CDCl_3$) 8.61-8.59 (m, 1H), 8.39 (d, 8 Hz, 1H), 8.29-8.24 (m, 1H), 7.99 (d, 8 Hz, 2H), 7.86-7.82 (m, 1H), 7.67-7.62 (m, 1H), 7.49 (d, 8Hz, 1H), 7.46-7.40 (m, 1H), 7.16-7.10 (m, 1H), 4.89-4.84 (m, 1H), 1.65 (d, 6 Hz, 1H).

Compound AB Sch 425741: ^{1}H NMR (300 MHz, $CDCl_3$) 8.88-8.86 (m, 1H), 8.62-8.59 (m, 1H), 8.30-8.29 (m, 1H), 8.15-8.11 (m, 1H), 8.00-7.96 (m, 2H), 7.71-7.63 (m, 1H), 7.56-7.52 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 4.99-4.84 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.54 (d, 7Hz, 3H).

Compound AT Sch 442333: ^{1}H NMR (300 MHz, $CDCl_3$) 8.51 (br s 1H), 8.39 (d, 8 Hz, 2H), 7.99 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.61-7.50 (m, 1H), 7.49 (d, 8 Hz), 7.05-6.99 (m, 1H), 4.70-4.50 (m, 2H), 2.83 (s, 3H), 2.57 (s, 3H), 1.50 (d, 7 Hz, 3H).

Compound BA SCH 414568: 1H NMR (300 MHz, $CDCl_3$) 1.54 (d, J = 6.9 Hz 3H), 2.7 (s, 3H), 4.72 (q, J = 5.5Hz 1H), 5.05 (br. d, J = 5Hz,1H, NH), 7.1 -8.55 (m, 11H).

Compound BD Sch 483018: ^{1}H NMR (300 MHz, $CDCl_3$) 8.51 (d, 9 Hz, 1H), 8.47-8.45 (m, 1H), 8.01-7.97 (m, 2H), 7.71-7.63 (m, 2H), 7.52-7.41 (m, 3H), 7.17-7.10 (m, 1H), 5.51 (d, 8 Hz, 1H), 4.90-4.80 (m, 1H), 1.64 (d, 7 Hz, 3H).

Compound BZ Sch 425801: ^{1}H NMR (300 MHz, $CDCl_3$) 8.43 (br s, 1H), 8.32 (d, 8 Hz, 1H), 8.28-8.22 (m, 1H), 7.94 (d, 8 Hz, 2H), 7.68-7.58 (m, 2H), 7.47-7.37 (m, 3H), 7.12-7.06 (m, 1H), 5.72 (d, 8 Hz, 1H), 4.86-4.70 (m, 1H), 2.59 (s, 3H), 1.60 (d, 7 Hz, 3H).

Compound CD Sch 357520: ^{1}H NMR (300 MHz, $CDCl_3$): 8.82-8.78 (m, 1H), 8.23 (d, 7 Hz, 2H), 8.21-8.07 (m, 1H), 7.81-7.77 (m, 2H), 7.63-7.57 (m, 1H), 7.55 (d, 7 Hz, 2H), 7.40-7.32 (m, 1H), 7.20-7.16 (m, 1H), 4.8-4.7 (m, 2H), 2.67 (s, 3H), 1.55 (d, 7 Hz, 2H).

Compound FS Sch 412570: ^{1}H NMR (300 MHz, $CDCl_3$) 8.66-8.62 (m, 1H), 8.51-8.47 (m, 1H), 8.29-8.24 (m, 1H), 7.99-7.95 (m, 2H), 7.93-7.89 (m, 2H), 7.67-7.53 (m, 1H), 7.50-7.44 (m, 2H), 7.42-7.39 (m, 1H), 7.13-7.07 (m, 1H), 4.78-4.73 (m, 1H), 4.61-4.59 (m, 1H), 2.70 (s, 3H), 1.56 (d, 7 Hz, 3H).

Compound FY Sch 442680: ^{1}H NMR (300 MHz, $CDCl_3$) 8.66-8.63 (m, 1H), 8.49-8.46 (m, 1H), 8.28-8.25 (m, 1H), 8.01 (d, 8 Hz, 2H), 7.93-7.89 (m, 2H), 7.65-7.58 (m, 1H), 7.56 (d, 8 Hz, 2H), 7.47-7.41 (m, 1H), 7.13-7.07 (m, 1H), 5.18 (d, 6 Hz, 1H), 4.90-4.80 (m, 1H), 1.66 (d, 7 Hz, 3H).

Compound GG Sch 487885: ^{1}H NMR (300 MHz, $CDCl_3$): 8.88 (d, 1.2 Hz, 1H), 8.51-8.56 (m, 2H), 8.31 (dd, 8 Hz, 1Hz, 1H), 8.18 (dd, 8 Hz, 1 Hz, 1H), 8.08-7.96 (m, 3H), 7.62-7.48 (m, 3H), 5.51 (d, 9 Hz, 1H), 4.90-4.70 (m, 1H), 1.62 (d, 7 Hz, 3H).

Compound GH Sch 487886: ^{1}H NMR (300 MHz, $CDCl_3$): 8.63 (d, 2 Hz), 8.58-8.55 (m, 1H), 8.34-8.28 (m, 2H), 8.07-7.98 (m, 3H), 8.35 (dd, 8 Hz, 2 Hz, 1H), 7.55-7.46 (m, 3H), 5.34 (d, 8 Hz, 1H), 4.9-4.8 (m, 1H), 1.64 (d, 6 Hz, 3H).

Compound GQ/XXIX, Sch 508195: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56-8.52 (m, 1H), 8.32-8.21 (m, 3H), 8.02-7.92 (m, 4H), 5.42 (d, 9 Hz, 1H), 8.02-7.92 (m, 4H), 5.42 (d, 1H, 9 Hz), 4.84-4.78 (m, 1H), 2.16-2.06 (m, 1H), 1.60 (d, 7Hz, 3H), 1.20-1.17 (m, 2H), 0.97-0.89 (m, 1H).

Compound GR/XXX, Sch 507686: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33-8.22 (m, 3H), 8.00-7.94 (m, 2H), 7.66-7.58 (m, 1H), 7.53-7.37 (m, 4H), 7.16-7.05 (m, 1H), 5.160 (d, 9 Hz, 1H), 4.88-4.83 (m, 1H), 2.17-2.06 (m, 1H), 1.65 (d, 7 Hz, 3H), 1.28-1.20 (m, 2H), 0.97-0.90 (m, 2H).

Compound GS/XXXI, Sch 543473: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38-8.29 (m, 2H), 8.17 (d, 8 Hz, 1H), 8.07-8.02 (m, 1H). 7.91-7.85 (m, 2H), 7.56-7.36 (m, 5H), 6.11 (d, 8 Hz, 1H), 4.84-4.78 (m, 1H), 2.12-2.01 (m, 1H), 1.57 (d, 7Hz, 3H), 1.21-1.12 (m, 2H), 0.92-0.86 (m, 2H).

Compound GW/XXXVI, Sch 525814 : ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (d, 7.8 Hz, 1H), 8.27-8.42 (m, 4H), 8.13 (dd, 7.8 Hz, 2.1 Hz, 1H), 7.93 (d, 8.4 Hz, 2H), 7.78-7.63 (m, 2H), 7.59 (d, 8.4 Hz, 2H), 4.80 (m, 1H), 1.44 (d, 6.9 Hz, 3H).

Compound HO/XXXXXV, Sch 515552 : ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, 3.9 Hz, 1H), 8.31-8.22 (m, 2H), 8.124 (d, 2.7 Hz, 1H), 8.05-7.95 (m, 1H), 7.92 (d, 8.4 Hz, 2H), .750-7.45 (m, 1H), 7.92 (d, 8.4 Hz, 2H), 7.27-7.23 (m, 2H), 5.8 (d, NH, 1H), 4.85-4.75 (m, 1H), 3.99 (s, 3H), 1.58 (d, 7.2 Hz, 3H).

Compound HP/XXXXXVI, Sch 541887: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56-8.52 (m, 1H), 8.31-8.23 (m, 3H), 8.02-7.90 (M, 4H), 4.87-4.78 (d, 7 Hz, 1H), 4.69 (m, 1 H), 2.66 (s, 3H), 2.16-2.06 (m, 1H), 1.51 (d, 7 Hz, 3H), 1.27 –1.17 (m, 2H), 0.96-0.90 (m, 2H).

The compounds of the present invention exhibit anti-inflammatory and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, psoriasis, allergy, inflammatory disorders of the lungs and gastrointestinal tract such as Crohn's disease, and respiratory tract disorders such as reversible airway obstruction, asthma, chronic obstructive pulmonary disease (COPD)

and bronchitis. This utility is manifested as demonstrated by activity in the following assay.

Potential cannabinoid receptor ligands were screened for the ability to compete with [^{3}H] CP-55,940 for binding to recombinant cannabinoid receptors. Test compounds were serially diluted in Diluent Buffer (50 mM Tris pH 7.1, 1 mM EDTA, 3 mM $MgCl_2$, 0.1% BSA, 10% DMSO, 0.36% methyl cellulose (Sigma M-6385)) from stocks prepared in 100% DMSO. Aliquots (10 ul) were transferred into 96-well microtiter plates. Membrane preparations of recombinant human cannabinoid CB2 receptor (Receptor Biology #RB-HCB2) or recombinant human cannabinoid CB1 receptor (Receptor Biology #RB-HCB1) were diluted to 0.3 mg/ml in Binding Buffer (50 mM Tris pH 7.2, 1 mM EDTA, 3 mM $MgCl_2$, 0.1% BSA). Aliquots (50 ul) were added to each well of the microtiter plate. The binding reactions were initiated by addition of [^{3}H] CP-55,940 (New England Nuclear # NET 1051; specific activity =180 Ci/mmol) to each well of the microtiter plate. Each 100 ul reaction mixture contained 0.48 nM [^{3}H] CP-55,940, 15 ug membrane protein in binding buffer containing 1% DMSO and 0.036 % methyl cellulose. Following incubation for 2 hours at room temperature, the reactions were filtered through 0.5% polyethylenimine-coated GF/C filter plates (UniFilter-96, Packard) with a TomTec Mark 3U Harvester (Hamden, CT). The filter plate was washed 5 times with binding buffer, rotated 180°, then re-washed 5 times with binding buffer. Bound radioactivity was quantitated following addition of 30 ul of Packard Microscint 20 scintillant in a Packard TopCount NXT microplate scintillation counter. Non-linear regression analysis of the resulting data was performed using Prism 2.0b (GraphPad, San Diego, CA).

Cannabinoid receptor ligands according to the present invention have anti-inflammatory activity and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) or

bronchitis. It is contemplated that a compound of this invention may be useful in treating more than one of the diseases listed.

Additionally, one or more compounds of the present invention can be co-administered or used in combination with one or more disease-modifying antirheumatic drugs (DMARDS) such as methotrexate, azathioptrine leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. One or more compounds of the invention can also be co-administered with or used in combination with one or more NSAIDS such as piroxicam, naproxen, indomethacin, ibuprofen and the like; one or more COX-2 selective inhibitors such as Vioxx® and Celebrex®; one or more COX-1 inhibitors such as Feldene; immunosuppressives such as steroids, cyclosporine, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel, Remicade, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production. Other drugs that the compounds of the invention can be co-administered or used in combination with include Anaprox, Arava, Arthrotec, Azulfidine, Aspirin, Cataflam, Celestone Soluspan, Clinoril, Cortone Acetate, Cuprimine, Daypro, Decadron, Depen, Depo-Medrol, Disalcid, Dolobid, Naprosyn, Gengraf, Hydrocortone, Imuran, Indocin, Lodine, Motrin, Myochrysine, Nalfon, Naprelan, Neoral, Orudis, Oruvail, Pediapred, Plaquenil, Prelone, Relafen, Solu-Medrol, Tolectin, Trilisate and/or Volataren. These include any formulation of the above named drugs.

For the treatment of multiple sclerosis, one or more compounds of the invention can be co-administered or used in combination with Avonex, Betaseron and/or Copaxone.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agents.

The present invention also relates to a pharmaceutical composition comprising one or more compounds of formula I and one or more pharmaceutically acceptable carriers. The compounds of formula I can be administered in any conventional

dosage form known to those skilled in the art. Pharmaceutical compositions containing the compounds of formula I can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like. All routes of administration are contemplated including, but not limited to, parenteral, transdermal, subcutaneous, intramuscular, sublingual, inhalation, rectal and topical.

Thus, appropriate unit forms of administration include oral forms such as tablets, capsules, powders, cachets, granules and solutions or suspensions, sublingual and buccal forms of administration, aerosols, implants, subcutaneous, intramuscular, intravenous, intranasal, intraoccular or rectal forms of administration.

When a solid composition is prepared in the form of tablets, e.g., a wetting agent such as sodium lauryl sulfate can be added to micronized or non-micronized compounds of formula I and mixed with a pharmaceutical vehicle such as silica, gelatin starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, various polymers, or other appropriate substances. Tablets can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously or at predetermined intervals, e.g., by using ionic resins and the like.

A preparation in the form of gelatin capsules may be obtained, e.g., by mixing the active principle with a diluent, such as a glycol or a glycerol ester, and incorporating the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir can contain the active principle together, e.g., with a sweetener, methylparaben and propylparaben as antiseptics, flavoring agents and an appropriate color.

Water-dispersible powders or granules can contain the active principle mixed, e.g., with dispersants, wetting agents or suspending agents, such as polyvinylpyrrolidone, as well as with sweeteners and/or other flavoring agents.

Rectal administration may be provided by using suppositories which may be prepared, e.g., with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

Parenteral, intranasal or intraocular administration may be provided by using, e.g., aqueous suspensions, isotonic saline solutions or sterile and injectable solutions containing pharmacologically compatible dispersants and/or solubilizers, for example, propylene glycol or polyethylene glycol.

Thus, to prepare an aqueous solution for intravenous injection, it is possible to use a co-solvent, e.g., an alcohol such as ethanol or a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such as Tween® 80. An oily solution injectable intramuscularly can be prepared, e.g., by solubilizing the active principle with a triglyceride or a glycerol ester.

Topical administration can be provided by using, e.g., creams, ointments or gels.

Transdermal administration can be provided by using patches in the form of a multilaminate, or with a reservoir, containing the active principle and an appropriate solvent.

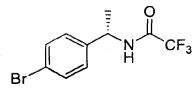
Administration by inhalation can be provided by using, e.g., an aerosol containing sorbitan trioleate or oleic acid, for example, together with trichlorofluoromethane, dichlorofluoromethane, dichlorotetrafluoroethane or any other biologically compatible propellant gas; it is also possible to use a system containing the active principle, by itself or associated with an excipient, in powder form.

The active principle can also be formulated as microcapsules or microspheres, e.g., liposomes, optionally with one or more carriers or additives.

Implants are among the prolonged release forms which can be used in the case of chronic treatments. They can be prepared in the form of an oily suspension or in the form of a suspension of microspheres in an isotonic medium.

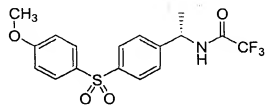
The daily dose of a compound of formula I for treatment of a disease or condition cited above is about 0.001 to about 100 mg/kg of body weight per day, preferably about 0.001 to about 10 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 0.1 to about 700 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

EXAMPLE I



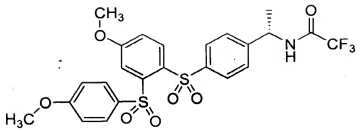
Compound 1

Compound 1. TFAA (67 mL, 0.474 mol) was dissolved in CH_2Cl_2 (300 mL) and cooled in an ice water bath. A solution of (S)-α-methylbenzylamine (56.4 g, 0.465 mol) dissolved in CH_2Cl_2 (100 mL) was added and the ice bath was removed. The reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled in an ice bath and MsOH (80 mL, 1.23 mol) was added followed by DBDMH (65 g, 0.227 mol). The reaction mixture was left stirring overnight at rt then quenched with 1M aq $NaHSO_3$. The organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated to give 130 g of white solid. The crude product was recrystallized from Et_2O and hexanes giving 46 g (32%) of intermediate Compound 1 as a solid.



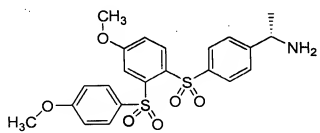
Compound 2

Compound 2. In a flame dried flask under N_2 blanket, Compound 1 (12.35 g, 41.2 mmol) was dissolved in dry THF (165 mL) and cooled to –78°C. Methyllithium (1.4 M in Et_2O, 30 mL, 42 mmol) was added and the reaction mixture was stirred for 5 min. n-BuLi (1.6 M in hexanes, 26 mL, 42 mmol) was added followed after 10 min by p-methoxybenzenesulfonyl fluoride (8.64 g, 45.4 mmol) which was prepared by standard methods. The cold bath was removed after 10 min and the reaction mixture was allowed to warm to rt over 45 min then quenched with pH 7 sodium phosphate buffer (1 M, 100 mL, 100 mmol). The reaction mixture was extracted with EtOAc and the resulting organic layer was washed with brine and dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by sgc (20%-50% EtOAc/hexanes gradient) to give 10.39 g (65%) of Compound 2 as a solid.



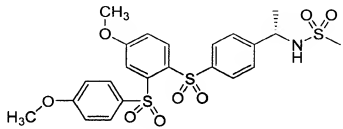
Compound 3

Compound 3. In a flame dried flask under N_2 blanket, Compound 2 (11.09 g, 28.6 mmol) was dissolved in anhyd THF (100 mL) and cooled to –78°C. A solution of n-BuLi (2.5 M in hexanes, 24 mL, 60 mmol) was added and the reaction mixture was stirred for 40 min. Bis-4-methoxyphenyl disulfide (8.76 g / 31.5 mmol) was added and the reaction mixture was stirred at –78 °C for 40 min then between –15 °C and –30 °C for 5 h then quenched with pH 7.0 sodium phosphate buffer (1.0 M, 120 mL). The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with additional EtOAc. The combined organic layer was washed with aq Na_2CO_3 and brine, then dried with $MgSO_4$ and concentrated to dryness. The crude product (13.8 g yellow foam) was dissolved in CH_2Cl_2 (120 mL) and cooled to 0°C. MCPBA (18.5 g, ca 107 mmol) was added, followed by additional CH_2Cl_2 (40 mL). The ice bath was removed and the reaction mixture was stirred at rt for overnight. Aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 were added and the layers were separated. The organic layer was washed with aq $NaHSO_3$, $NaHCO_3$, H_2O, and brine then dried with $MgSO_4$. The crude product was purified by sgc (30% to 50% EtOAc/hexanes gradient) to give 7.21 g (45%) of Compound 3.



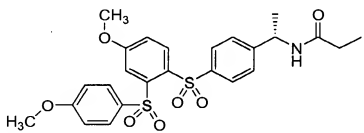
Compound 4

Compound 4. Compound 3 (4.47 g, 8.02 mmol) was dissolved in p-dioxane (16 mL) and cooled to 0 °C. LiOH (1.0 M aq, 10 mL, 10 mmol) was added and the ice bath was removed. The reaction mixture was stirred at rt for 6 h then concentrated. CH_2Cl_2 (100 mL) and NaOH (1.0 M aq, 10 mL) were added and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by sgc (2%-10% MeOH (NH_3)/CH_2Cl_2 gradient mobile phase) to give 3.23 g (87%) of Compound 4.



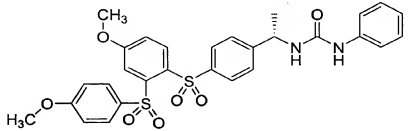
Compound I

Compound I. Compound 4 (3.08 g, 6.67 mmol) was dissolved in CH_2Cl_2 (33 mL) and triethylamine (1.40 mL, 10.0 mmol) then cooled to 0 °C. MsCl (569 μL, 7.34 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h and 15 min. Citric acid (0.5 M, 40 mL) and additional CH_2Cl_2 were added and the layers were separated. The organic layer was washed with citric acid, $NaHCO_3$, and brine then dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by sgc (40%-70% EtOAc/hexanes gradient) to give 3.44 g (96%) of Compound I as a solid.



Compound II

Compound II. Compound 4 (27.5 mg, 0.0595 mmol) was dissolved in methylene chloride (226 μL) and DIPEA (12 μL). A solution of propionyl chloride dissolved in 1,2-dichloroethane (1 M, 75 μL, 0.075 mmol) was added and the reaction mixture was shaken at room temperature overnight. Tris(2-aminoethyl)amine polystyrene (4.1 mmol N/g, ca 60 mg) was added to the reaction mixture. The reaction mixture was shaken for an additional hour at rt. The crude product was concentrated, then dissolved in EtOAc and filtered through a silica-gel SepPak (Waters Corp.). The resulting filtrate was concentrated to give 9 mg (29%) of Compound II.

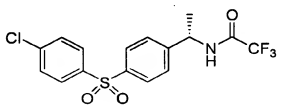


Compound III

Compound III. Compound 4 (25 mg, 0.054 mmol) was dissolved in CH_2Cl_2 (270 μL). A solution of phenyl isocyanate dissolved in toluene (1.0 M, 65 mL, 0.065 mmol) was added and the reaction mixture was shaken at rt overnight. Tris (2-aminoethyl) amine polystyrene (4.1 mmol N/g, ca 60 mg) was added to the reaction mixture and the reaction mixture was shaken for an additional 40 min at rt. EtOAc was added and the reaction mixture was filtered through a silica gel SepPak (Waters Corp.). The resulting filtrate was concentrated to give 18 mg (57%) of Compound III.

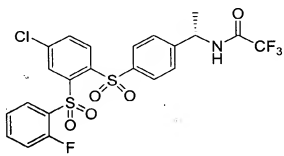
EXAMPLE II

Preparation of Sch 356036, Sch 414319, and Sch 442680



Compound 5

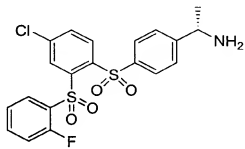
Compound 5. In a 3-necked flame-dried flask under N_2 blanket Compound 1 (40.0 g, 134 mmol) was dissolved in anhyd THF (535 mL) and cooled to –75 °C (internal temperature). A solution of methyllithium (1.4 M in diethyl ether, 105 mL, 147 mmol) was added at a rate that kept the internal temperature below -60 °C. The reaction was stirred for 15 min and a solution of n-BuLi (2.5 M in hexanes, 62 mL, 155 mmol) was added at a rate that maintained the internal temperature of the reaction below –65 °C. The reaction mixture was stirred for 40 min. and a solution of bis(4-chlorophenyl) disulfide (42 g, 146 mmol) dissolved in anhyd THF (90 mL) was added via addition funnel over 1 h. The reaction mixture was stirred for 3 h then quenched with HCl (1 M aqueous, 200 mL, 200 mmol). EtOAc (500 mL) was added and the layers were separated. The aqueous layer was extracted with 500 mL EtOAc, and the combined organic layer was washed with 1 M aq KOH, water, and brine. After drying with $MgSO_4$, the solvent was evaporated to give 54.1 g of a solid. The crude product (52.3 g) was dissolved in CH_2Cl_2 (750 mL) and cooled to 2 °C (internal temp). MCPBA (60%, 184 g) was added in portions over 1 hr and 20 min keeping the internal temperature below 15 °C. The reaction mixture was stirred an additional 2 h. NaOH (1 M aq, 500 mL) and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with an additional 300 mL of CH_2Cl_2. The combined organic layer was washed with 1M aqueous NaOH, water, and brine, then dried with $MgSO_4$. After evaporation of the solvent, a solid (65 g) was obtained. The crude product was partially purified by trituration from Et_2O/hexanes to give 33.3 g of a solid which was subsequently purified via sgc (20%-25% EtOAc/hexanes) to give 30 g (57%) of Compound 5 as a solid.



Compound 6

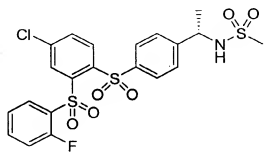
Compound 6. In a flame dried 3-necked flask under N_2 blanket Compound 5 (44 g, 112 mmol) was dissolved in anhyd THF (450 mL) and cooled in a dry ice/IPA bath. A solution of n-butyl lithium (2.5 M in hexanes, 92 mL, 230 mmol) was added at a rate that maintained the internal reaction temperature below –60 °C, and the

reaction mixture was stirred for 1 h. A solution of 2-fluorobenzenesulfonyl fluoride (22.3 g, 125 mmol) dissolved in anhyd THF (20 mL) was added and the reaction mixture was left stirring overnight and allowed to warm to rt. The reaction mixture was cooled to 0 °C and quenched with saturated aq ammonium chloride (300 mL). EtOAc (600 mL) and brine (25 mL) were added and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. The solvents were evaporated giving a foam (62 g). The product was purified by sgc (20%-25% EtOAc/hexanes mobile phase) giving 9.1 g (15%) of Compound 6.



Compound 7

Compound 7. Compound 6 (6.77 g, 12.3 mmol) was dissolved in dioxane (15 mL) and cooled in an ice bath. Aqueous lithium hydroxide (1 M, 15 mL, 15 mmol) was added and the reaction mixture was left stirring overnight. The reaction mixture was concentrated, then partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$. Evaporation of the solvent afforded 5.66 g of a foam which was purified by sgc (10% MeOH (NH_3)/CH_2Cl_2) to give 4.27 g of Compound 7 (77%).

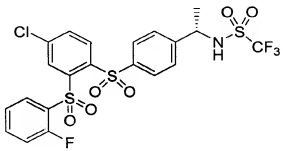


Compound IV

Compound IV. Compound 7 (2.66 g, 5.86 mmol) was dissolved in CH_2Cl_2 (28 mL) and triethylamine (0.98 mL) and cooled to 0°C. MsCl (0.499 mL, 6.45 mmol) was

added and the reaction mixture was stirred at 0 °C for 6 h. The reaction mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$. Evaporation of the solvent afforded 3.0 g of a foam which was purified by sgc (40%-50% EtOAc/hexanes gradient) to give 2.77 g (89%) of Compound IV.

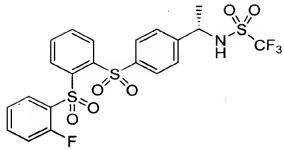
Compound IV Sch 356036: ^{1}H NMR (300 MHz, $CDCl_3$) 8.61-5.97 (m, 2H), 8.40 (d, 8 Hz, 1H), 8.24-8.21 (m, 1H), 7.96 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.70-7.63 (m, 1H), 7.52 (d, 8 Hz, 2H), 7.46-7.40 (m, 1H), 7.18-7.12 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.56 (d, 7Hz, 3H).



Compound V

Compound VSch 414319. Compound 7 (26.1 g, 57.4 mmol) was dissolved in CH_2Cl_2 (200mL) and triethylamine (20 mL) and cooled to –78°C. Triflic anhydride (10.45 mL, 62.1 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched with water and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. The solvent was evaporated to give 42 g of a foam. The crude product was purified *via* sgc (33%-50% EtOAc/hexanes gradient) to give 29.7 g (88%) of Compound V.

Compound V Sch 414319: ^{1}H NMR (300 MHz, $CDCl_3$) 8.61-8.59 (m, 1H), 8.39 (d, 8 Hz, 1H), 8.29-8.24 (m, 1H), 7.99 (d, 8 Hz, 2H), 7.86-7.82 (m, 1H), 7.67-7.62 (m, 1H), 7.49 (d, 8Hz, 1H), 7.46-7.40 (m, 1H), 7.16-7.10 (m, 1H), 4.89-4.84 (m, 1H), 1.65 (d, 6 Hz, 1H).

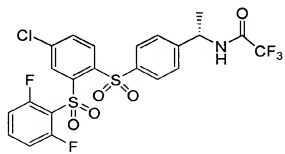


Compound VI

Compound VI. Compound V (300 mg, 0.512 mmol) was dissolved in methanol (60 mL). Sodium bicarbonate (720 mg, 8.57 mmol) and 5% palladium on carbon (480 mg) were added. The reaction mixture was shaken on a Parr apparatus under 52 psi of hydrogen gas overnight. The reaction mixture was filtered and the solvent was evaporated. The resulting material was partitioned between EtOAc and aq $NaHCO_3$. The organic layer was dried with $MgSO_4$ and the solvents were evaporated. The crude product was purified *via* sgc (33% EtOAc/hexanes) to give 257 mg (91%) of Compound VI.

EXAMPLE III

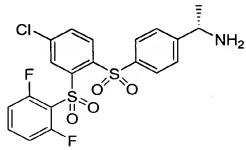
Preparation of Sch 414428



Compound 8

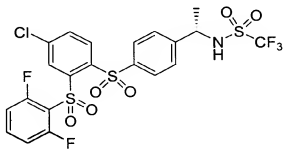
Compound 8. In a flame dried 3-necked flask under N_2 blanket Compound 5 (35.7 g, 91 mmol) was dissolved in anhyd THF (360 mL) and cooled in a dry ice/IPA bath. A solution of n-BuLi (2.5 M in hexanes, 76 mL, 190 mmol) was added at a rate that maintained the internal temperature below –60 °C. The reaction mixture was stirred for 1 h. A solution of 2,6-difluorobenzenesulfonyl fluoride (19.47 g, 99.28 mmol) dissolved in anhyd THF (60 mL) was added. The reaction mixture was stirred for 2.5 h, then quenched with saturated aq NH_4Cl (400 mL). EtOAc (500 mL) was

added and the layers were separated. The aq layer was extracted with EtOAc and the combined organic layer was washed with brine and dried with $MgSO_4$. The solvent was evaporated to give 60.7 g of an oil which was purified by sgc (15%-40% EtOAc/hexanes gradient) giving 14.4 g (28%) of Compound 8.



Compound 9

Compound 9. Compound 8 (21.1 g, 37.2 mmol) was dissolved in dioxane (47 mL) and aq lithium hydroxide (1.0 M, 41 mL, 41 mmol) was added. After 5.5 h, additional LiOH (20 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was extracted with CH_2Cl_2, and partitioned between CH_2Cl_2 and water. The aq layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$. The solvents were evaporated to give 17.6 g of a foam and the crude product was purified by sgc (1%-3% MeOH (NH_3)/CH_2Cl_2 gradient) to give 12.2 g (69%) of Compound 9.



Compound VII

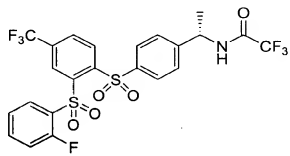
Compound VII. Compound 9 (10.7 g, 22.6 mmol) was dissolved in a mixture of CH_2Cl_2 (90 mL) and triethylamine (8mL) and cooled to –78 °C. Triflic anhydride (3.80 mL, 22.6 mmol) was added and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aq $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was

washed with brine and dried with $MgSO_4$. The solvents were evaporated and the crude product was purified by sgc to give 9.88 g (73%) of Compound VII.

EXAMPLE IV

Preparation of Sch 425742

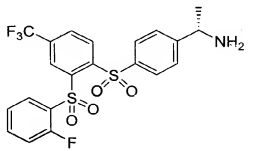
Compound 5. In a flame dried flask under N_2 blanket Compound 1 (39.2 g, 132 mmol) was dissolved in anhyd THF (1 L) and cooled in a dry ice/acetone bath. A solution of methyllithium (1.6 M in Et_2O, 82.7 mL, 132 mmol) was added followed by a solution of n-BuLi (2.5 M in hexanes, 53 mL, 133 mmol). The reaction mixture was stirred for 25 min and a solution of bis(4-trifluoromethylphenyl) disulfide (46.9 g,132 mmol) dissolved in THF (200 mL) was added. The reaction mixture was stirred for 2 h then allowed to warm to rt overnight. The reaction was quenched with water and concentrated. The resulting mixture was diluted with EtOAc, washed with water, and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified via sgc (20% EtOAc/hexanes) to give 49.2 g (95%) of a solid. This material (49.2 g) was dissolved in CH_2Cl_2 (1.2 L) and cooled in an ice bath. MCPBA (60%, 90 g) was added in small portions. After 1 h, the ice bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous $NaHCO_3$. The combined organic layer was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified by sgc (25% EtOAc/hexanes) to give 46.3 g (85%) of Compound 5.



Compound 10

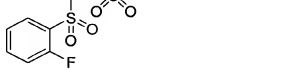
Compound 10. In a flame dried flask under N_2 blanket, Compound 5 (21.55 g, 50.7 mmol) was dissolved in anhyd THF (300 mL) and cooled in a dry ice/IPA bath. A solution of methyllithium (1.6 M in Et_2O, 32 mL, 51 mmol) was added, followed by n-

BuLi (2.5 M in hexanes, 20.3 mL, 50.7 mmol) and the reaction mixture was stirred for 10 min. A solution of bis-(2-fluorophenyl) disulfide (14.2 g, 55.7 mmol) dissolved in THF was added and the reaction mixture was stirred for 2 h at –78°C. The ice bath was removed and the reaction mixture was allowed to warm to rt and left stirring overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified via sgc (25% EtOAc/hexanes) to give 23.2 g of a solid. This material was dissolved in CH_2Cl_2 (400 mL) and cooled in an ice bath. MCPBA (60%, 30.3 g) was added in several portions and the reaction mixture was stirred for 1 h. The ice bath was removed and the reaction mixture was left stirring overnight. The reaction mixture was partitioned between CH_2Cl_2 and 5% aq Na_2CO_3. The organic layer was washed with water and dried with Na_2SO_4. The solvents were evaporated and the crude product was purified *via* sgc (25%EtOAc/hexanes) to give 10.84 g (44%) of Compound 10.



Compound 11

Compound 11. Compound 10 (11.88 g, 20.36 mmol) was dissolved in dioxane (200 mL) and aq lithium hydroxide (1.0 M, 400 mL) was added. The reaction mixture was stirred for 3 h then and partitioned between CH_2Cl_2 and water. The organic layer was dried with Na_2SO_4 and concentrated to give 9.34 g (99%) of Compound 11.



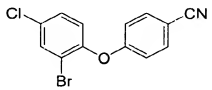
Compound VIII

Compound VIII. Compound 11 (0.63 g, 1.29 mmol) was dissolved in a mixture of CH_2Cl_2 (60mL) and triethylamine (0.27 mL) and cooled in an ice bath. Triflic anhydride (0.55 g, 1.95 mmol) was added and the reaction mixture was stirred for 1 h. The ice bath was removed, and the reaction mixture was stirred an additional 3 h. The reaction was partitioned between water and CH_2Cl_2. The organic layer was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified by sgc (20% EtOAc/hexanes) to give 0.53 g (66%) of Compound VIII.

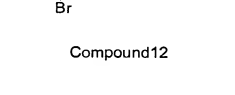
Compound VIII Sch 425742: ^{1}H NMR (300 MHz, $CDCl_3$) 8.89-8.87 (m, 1H), 8.58 (d, 8Hz, 1H), 8.32-8.25 (m, 1H), 8.15-8.11 (m, 1H), 8.03-7.98 (m, 2H), 7.71-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 5.62 (d, 8 Hz, 1H), 4.90-4.80 (m, 1H), 1.63 (d, 7 Hz, 3H).

EXAMPLE V

Preparation of Sch 443908

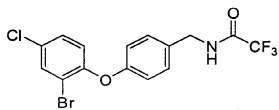


Potassium hydroxide (3.1 g, 55.2 mmol), 2-bromo-4-chlorophenol (9.52 g, 45.9 mmol), and 4-fluorobenzonitrile (5.73 g, 47.3 mmol) were added to DMA (25 mL) and the reaction mixture was stirred between 100 °C and 110 °C for one week. The reaction mixture was stirred at rt an additional two days. The solvents were partially removed on the rotary evaporator and the resulting mixture was partitioned between water and a 3:1 Et_2O/hexanes solution. The organic layer was washed with water and brine, then dried with $MgSO_4$. The solvents were evaporated and the crude product was purified by sgc (20%-30% CH_2Cl_2/hexanes) to give 11.96 g (81%) of an oil.



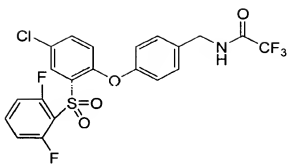
Compound12

Compound 12. The product of the above step (5.90 g, 19.1 mmol) was placed under N_2 atmosphere and a solution of borane in THF (1.0 M, 21 mL, 21 mmol) was added causing an exotherm. Once the reaction mixture had returned to rt, it was heated to reflux and stirred at reflux overnight. Additional borane in THF (1.0 M, 20 mL, 20 mmol) was added and the reaction mixture was stirred at reflux for a additional 26 h then allowed to cool to rt. Water (55 mL) was added and the reaction mixture was partially concentrated. The resulting mixture was partitioned between EtOAc and aq NaOH (1.0 M). The organic layer was dried with $MgSO_4$ and concentrated to give 6.2 g of an oil. This material was dissolved in Et_2O and a solution of HCl in Et_2O was added causing Compound 12 (5.2 g, 78%) to precipitate as a solid.



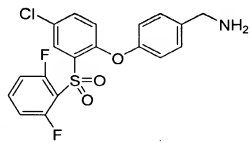
Compound 13

Compound 13. Compound 12 (5.13 g, 16.6 mmol) was suspended in a mixture of CH_2Cl_2 (40 mL) and triethylamine (7.5 mL). The mixture was cooled in an ice-water bath and TFAA (2.35 mL, 16.6 mmol) was added. The reaction mixture was stirred for 1 h and 20 min and the ice bath was removed. The reaction mixture was stirred for an additional 1 h and 20 min at rt. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with aq citric acid (0.5 M), saturated aq $NaHCO_3$, water, and brine, then dried with $MgSO_4$. The solvents were evaporated and the crude product (5.22 g) was purified *via* sgc (10%-20% EtOAc/hexanes gradient) to give Compound 13.



Compound 14

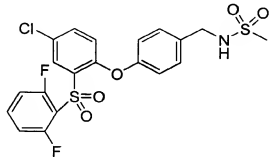
Compound 14. In a flame dried flask under N_2 blanket, Compound 13 (1.00 g, 2.47 mmol) was dissolved in anhyd THF (13 mL) and cooled in a dry ice/IPA bath. Methyllithium (1.4 M in Et_2O, 2.3 mL, 3.22 mmol) was added, followed by n-BuLi (2.5 M in hexanes, 1.3 mL, 3.25 mmol). The reaction mixture was stirred for 1 h at –78 °C. A solution of 2,6-difluorobenzenesulfonyl fluoride (1.10 g, 5.60 mmol) dissolved in THF was added and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with pH 7 sodium phosphate buffer (1.0 M) and EtOAc was added. The layers were separated and the aqueous layer was extracted with additional EtOAc. The combined organic layer was washed with brine and dried with $MgSO_4$. The solvents were evaporated and the crude product was purified via sgc (20%-33% EtOAc/hexanes) gradient to give 76 mg of Compound 14.



Compound 15

Compound 15. Compound 14 (59 mg, 0.12 mmol) was dissolved in 700 μL of dioxane and LiOH (1.0 M, 300 μL, 0.3 mmol) was added. The reaction mixture was stirred at rt for 24 h then partitioned between CH_2Cl_2 and 1.0 M aq NaOH. The organic layer was dried with $MgSO_4$ and concentrated. The crude product was

purified via PTLC (Merck- silica plates, 3% ($MeOH/NH_3$)/CH_2Cl_2) to give the desired Compound 15. (21 mg, 45%).

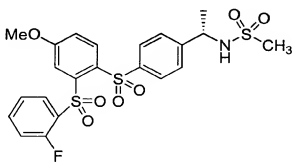


Compound IX

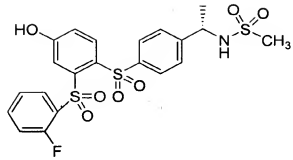
Compound IX. Compound 15 (17 mg, 0.042 mmol) was dissolved in CH_2Cl_2 (166 μL) and DIPEA (20 μL). The flask was cooled in an ice/water bath and MsCl (12 μL, 0.15 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and 30 min. The resulting mixture was partitioned between water and CH_2Cl_2. The organic layer was washed with water and brine, then dried with $MgSO_4$. The crude product was purified *via* PTLC (50 % EtOAc/hexanes) to give 10 mg (50%) Compound IX.

EXAMPLE VI

Preparation of Sch 412851



Compound 16



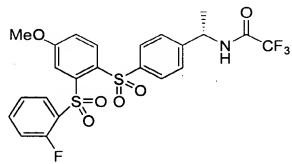
Compound X

Compound 16 (0.116 g, 0.22 mmoles) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. BBr_3 solution (1.0 M in CH_2Cl_2, 0.66 mL) was added and the ice bath was removed. The reaction mixture was stirred at rt for 48 h and then quenched with water at –78 °C. The reaction mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed with aqueous $NaHCO_3$, H_2O (3 X 5 mL), and brine. The organics were dried over Na_2SO_4 and the solvent was removed under vacuum to give 0.09 g of crude product. The product was isolated by PTLC (5% CH_3OH / CH_2Cl_2) to provide Compound X (0.01g, 8.8%).

Compound 16 SCH 412702: ^1H NMR (300 MHz, $CDCl_3$) 1.54 (d, J = 6.9Hz 3H), 2.67 (s, 3H), 4.72 (q, J = 5Hz 1H), 4.86 (br. d, J = 5Hz,1H, NH), 7.08-8.42 (m, 11H).

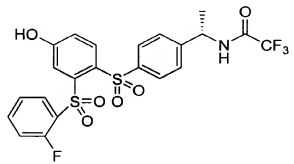
EXAMPLE VII

Preparation of Sch 414093

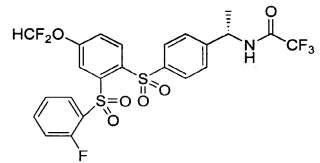


Compound 17

Compound 17 was converted to Compound 18 using the procedure in example VI.

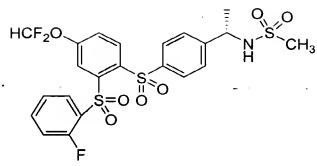


Compound 18



Compound 19

Compound 18 (0.34 g, 0.64 mmoles) was dissolved in DMF (11 mL), cesium carbonate (0.84 g, 2.58 mmol) was added and the reaction mixture was cooled to 15 °C. Dry bromodifluoromethane gas was introduced into the solution and bubbled for 15-20 min. Progress of the reaction was monitored by TLC and upon completion the reaction mixture was diluted with EtOAc (20 mL), washed with water (4 X 10 mL), and brine. The organics were dried over Na_2SO_4 and concentrated under reduced pressure to give 0.36 g of an oil. The crude product was purified by PTLC (50% EtOAc/hexanes) to provide 0.31 g (83%) of Compound 19.



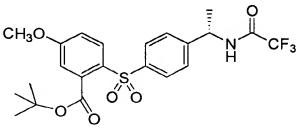
Compound XI

Compound 19 was converted to Compound XI using the procedure in example II.

Compound XI SCH 414093: ^1H NMR (400 MHz, $CDCl_3$) 1.51 (d, J = 7.2Hz 3H), 2.67 (s, 3H), 4.702 (q, J = 6.8Hz 1H), 5.05 (br. d, J = 6.4Hz,1H, NH), 6.71 (t, J = 71.6 Hz, CF2H) 7.07-8.47 (m, 11H).

EXAMPLE VIII

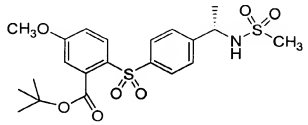
Preparation of Sch 416580



Compound 20

Compound 20. To a solution of Compound 2 (5.00 g, 12.9 mmol) in anhyd THF (75 mL) at –78 °C was added *n*-BuLi (13 mL, 2.5 M in hexanes, 32 mmol) dropwise over 10 min. The reaction mixture was stirred for 30 min. A solution of di-*t*-butyl dicarbonate (3.10 g, 14.2 mmol) in anhyd THF (25 mL) was added in one portion via cannula. The reaction was allowed to proceed for 4 h at –78 °C. The reaction mixture was then diluted with EtOAc (~250 mL) and washed successively with saturated aq $NaHSO_4$ (~100 mL), water (~100 mL), and brine (~100 mL). The organic layer was dried over anhyd $MgSO_4$, filtered, and concentrated under reduced pressure

to yield a solid. Further purification of the solid by sgc (25% EtOAc/hexanes) gave 5.32 g (84%) of Compound 20 as a solid.

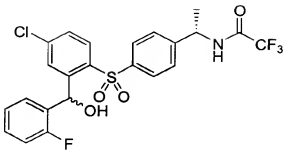


Compound XII

Compound XII. Compound 20 (2.06 g, 4.23 mmol) was dissolved in methanol (40 mL) and a solution of potassium carbonate (2.92 g, 21.1 mmol) in water (10 mL) was added. The reaction was allowed to proceed for 18 h. The solvent was then removed by evaporation under reduced pressure. The resulting white solid was partitioned between water (~100 mL) and EtOAc (~400 mL). The aqueous layer was extracted further with EtOAc (~100 mL). The combined organic layers were washed with brine (~500 mL), then dried over anhyd $MgSO_4$ and filtered. Evaporation of the solvent gave 1.22 g (74%) of *t*-butyl 2-[(4-(1(*S*)-aminoethyl)phenyl]sulfonyl-5-methoxybenzoate, an oil, which was used in the next step without further purification. MsCl (242 µL, 357 mg, 3.12 mmol) was added dropwise to a solution of crude *t*-butyl 2-[(4-(1(*S*)-aminoethyl)phenyl]sulfonyl-5-methoxybenzoate (1.22 g, 3.12 mmol) and triethylamine (522 µL, 379 mg, 3.75 mmol) in anhyd CH_2Cl_2 (3.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, then allowed to warm to rt, and subsequently stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2 (~50 mL) and washed successively with 1 M HCl (~50 mL), water (3 x ~50 mL) and brine (~50 mL). The organic solution was dried over anhyd $MgSO_4$, filtered, and concentrated to yield a solid. Subsequent purification of the crude product by sgc (25% EtOAc/hexanes) gave 1.41 g (96%) of Compound XII as a solid.

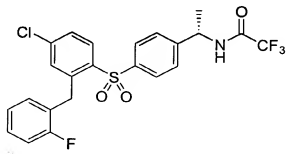
EXAMPLE IX

Preparation of Sch 414379



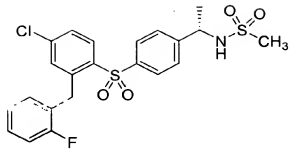
Compound 21

Compound 21. In a flame dried flask under N_2 blanket, Compound 5 (400 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and cooled to –78 °C. A solution of n-BuLi (1.0 M in hexanes, 1.9 mL, 1.9 mmol) was added and the reaction mixture was stirred for 30 min. 2-Fluorobenzaldehyde (200 mg, 1.6 mmol) was added and the reaction mixture was stirred at –78 °C for 3 h. The reaction mixture was then quenched with saturated aq NH_4Cl (20 mL). Methylene chloride (30 mL) was added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated to dryness. The crude product was purified via sgc (25% EtOAc/hexanes) to give 330 mg (62%) of Compound 21 as a powder.



Compound 22

Compound 22. Compound 21 (10 mg) was dissolved in CH_2Cl_2 (10 mL). Triethylsilane (40 µL, 0.25 mmol) was added followed by BF_3•Et_2O (20 µL, 0.16 mmol). The reaction mixture was stirred at rt overnight. After removing the solvent, the crude product was purified via PTLC (25% EtOAc/hexanes) to give 6.0 mg (62%) Compound 22 as an oil.

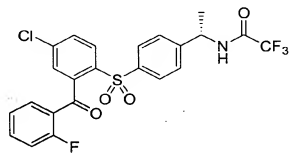


Compound XIII

Compound XIII. Compound 22 (12 mg) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed, CH_2Cl_2 (15 mL) and brine (15 mL) were added, and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. MsCl (14 μL, 0.18 mmol) was added followed by addition of pyridine (30 μL, 0.37 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and extracted. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (25% EtOAc/hexanes) to give 10 mg (86%) of Compound XIII as an oil.

EXAMPLE X

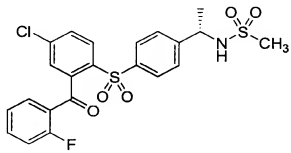
Preparation of Sch 414389, and Sch 415209



Compound 23

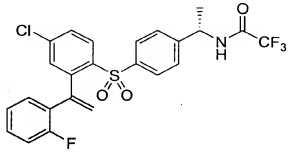
Compound 23. Compound 21 (330 mg, 0.64 mmol) was dissolved in CH_2Cl_2 (20 mL) at rt. Celite (450 mg) was added followed by addition of PCC (450 mg, 2.1 mmol). The mixture was stirred at rt overnight. The solid was removed by filtration and the organic layer was washed with aq. $NaHCO_3$ and brine. The organic layer was

dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via sgc (33% EtOAc/hexanes) to give 310 mg (94%) of Compound 23 as a powder.



Compound XIV

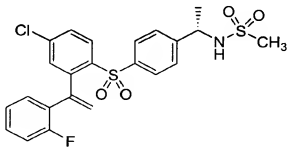
Compound XIV. Compound 23 (15 mg) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed and CH_2Cl_2 (15 mL) and brine (15 mL) were added and the layers separated. The aq layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. MsCl (15 μL, 0.19 mmol) was added followed by addition of pyridine (30 μL, 0.37 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and extracted. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (33% EtOAc/hexanes) to give 9 mg (62%) of Compound XIV as an oil.



Compound 24

Compound 24. Oven dried methyltriphenylphosphonium bromide (430 mg, 1.2 mmol) and LHDMS (1.0 M in hexanes, 1.8 mL, 1.8 mmol) were stirred in dry THF (5 ml) at 0 °C for 20 min., then warmed to rt and stirred for 10 min. A solution of

Compound 23 (300 mg, 0.58 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at rt overnight. EtOAc (20 ml) was added and the organic solution was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (25% EtOAc/hexanes) to give 260 mg (87%) of Compound 24 as an oil.

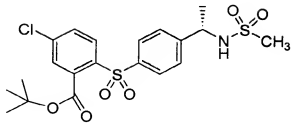


Compound XV

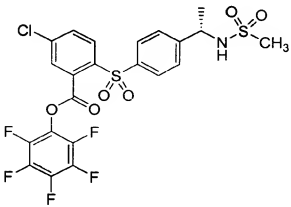
Compound XV. Compound 24 (200 mg, 0.39 mmol) was dissolved in methanol (3 mL) at rt. NaOH (1.0 M, 3 mL, 3.0 mmol) was added and the mixture was stirred at 50 °C for 2 h. The solvent was removed, CH_2Cl_2 (20 mL) and brine (20 mL) were added, and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. MsCl (200 μL, 2.5 mmol) was added followed by addition of pyridine (400 μL, 4.9 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and the organic layer separated, dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (50% EtOAc/hexanes) to give 160 mg (82%) of Compound XV as an oil.

EXAMPLE XI

Preparation of Sch 420411

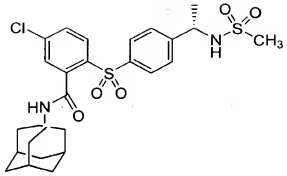


Compound 25



Compound 26

Compound 26. Compound 25 (1.3 g, 2.7 mmol) was stirred at rt with a mixture of CH_2Cl_2/TFA (2:1, 30 mL) for 3 h. The reaction mixture was then poured into brine (40 mL). The layers were separated. The aq layer was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was dissolved in CH_2Cl_2 (30 mL). EDCI (0.75 g, 3.9 mmol) and pentafluorophenol (0.73 g, 4.0 mmol) were added and the mixture was stirred at rt overnight. The reaction mixture was extracted with diluted aq NaOH and washed with brine. The organic layer was then dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via sgc (33% EtOAc/hexanes) to give 1.15 g (72%) of Compound 26 as a foam.

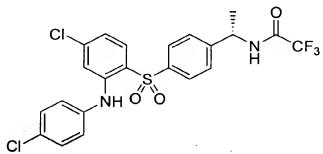


Compound XVI

Compound XVI. Compound 26 (50 mg) was dissolved in CH_2Cl_2 (2 mL). 1-Adamantanamine (21 mg, 0.14 mmol) was added followed by addition of DIPEA (0.05 mL, 0.29 mmol). The reaction mixture was shaken overnight. The reaction mixture was then subjected to Amberlyst 15 resin (300 mg, loading 4.1 mmol/g), and was again shaken overnight. The resin was removed by filtration. The filtrate was subjected to MP carbonate resin (Argonaut Technologies) (100 mg, loading 2.64 mmol/g) for 4 h. The resin was removed by filtration and the filtrate concentrated to give 33 mg (70%) of Compound XVI as a powder.

EXAMPLE XII

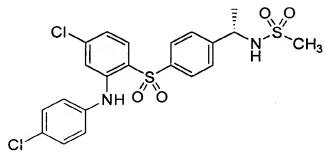
Preparation of Sch 413578, and Sch 414706



Compound 27

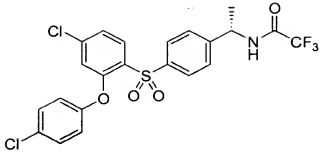
Compound 27. Compound 5 (500 mg, 1.3 mmol) was dissolved in dry THF (6 mL) at rt. NaH (53 mg, 60%, 1.3 mmol) was added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then cooled to –78 °C, and n-BuLi (1.0 M in hexanes, 1.5 mL, 1.5 mmol) was added dropwise under N_2 atmosphere. The reaction was stirred at –78 °C for 40 min. A solution of I_2 (390 mg, 1.5 mmol) in THF

(2 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h, then quenched with saturated aq NH_4Cl (20 mL). EtOAc (30 mL) was added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated to dryness. The crude product (640 mg) was used without further purification. The crude product (60 mg) was dissolved in toluene (2 mL) and $Pd(OAc)_2$ (2 mg), P^tBu_3 (1 drop), NaO^tBu (14 mg, 0.15 mmol) and *p*-Chloroaniline (13 mg, 0.11 mmol) were added. The mixture was kept in a sealed tube and heated to 120 °C for 20 h. After cooling, methylene chloride (30 mL) and brine (20 mL) were added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated to dryness. The crude product was purified with via PTLC (20% EtOAc/hexanes) to give 18 mg (30 %) of Compound 27 as a powder.



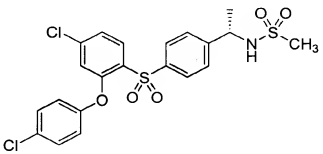
Compound XVII

Compound XVII. Compound 27 (12 mg) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 3 h. The solvent was removed, CH_2Cl_2 (20 mL) and brine (20 mL) were added, and the layers were separated. The aq layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (15mL) and cooled to 0 °C. MsCl (15 μL, 0.19 mmol) and pyridine (30 μL, 0.37 mmol) were added. The reaction mixture was slowly warmed up to rt and stirred overnight. Brine (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (33% EtOAc/hexanes) to give 6.0 mg (52%) of Compound XVII as an oil.



Compound 28

Compound 28. Compound 5 (500 mg, 1.3 mmol) was dissolved in dry THF (6 mL) at rt. NaH (53 mg, 60%, 1.3 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was cooled to –78 °C, and n-BuLi (1.0 M, 1.5 mL, 1.5 mmol) was added dropwise under N_2 atmosphere, and the temperature was maintained at –78 °C for 40 min. A solution of I_2 (390 mg, 1.5 mmol) in THF (2 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h. The reaction mixture was quenched with saturated aq NH_4Cl (20 mL). EtOAc (30 mL) was added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated to dryness. The crude product (640 mg) was used without further purification. The crude product (60 mg) was dissolved in toluene (2 mL) and NaH (5 mg, 60%, 0.12 mmol), $CuBr•Me_2S$ (34 mg, 0.17 mmol) and *p*-chlorophenol (15 mg, 0.12 mmol) were added. The reaction mixture was kept in a sealed tube and heated to 120 °C overnight. After cooling, CH_2Cl_2 (30 mL) and brine (20 mL) were added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated to dryness. The crude product was purified via PTLC (20% EtOAc/hexanes) to give 19 mg (31 %) of Compound 28 as a powder.

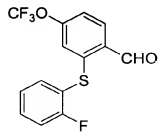


Compound XVIII

Compound XVIII. Compound 28 (15 mg, 29 μmol) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed and CH_2Cl_2 (20 mL) and brine (20 mL) was added and the layers were separated. The aq layer was extracted with additional CH_2Cl_2 (15 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (15mL) and cooled to 0 °C. MsCl (20 μL, 0.25 mmol) was added followed by addition of pyridine (20 μL, 0.25 mmol). The reaction mixture was slowly warmed up to rt and stirred overnight. Brine (15 mL) was added and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (50% EtOAc/hexanes) to give 7.0 mg (48%) of Compound XVII as an oil.

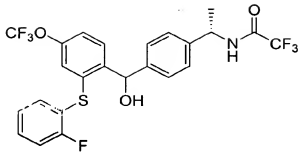
EXAMPLE XIII

Preparation of Sch 425084



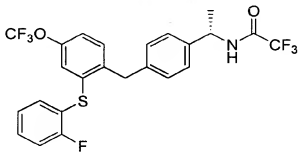
Compound 29

Compound 29. To a solution of N,N,N-Trimethylethylenediamine (1.2 mL, 8.6 mmol) in THF (8 mL) at –20 °C was added n-BuLi (1.6 M, 5.4 mL, 8.6 mmol) dropwise. After 15 min 4-trifluoromethoxybenzaldehyde (1.5 g, 7.8 mmol) in THF (8 mL) was added. The mixture was stirred for 15 minutes and additional n-BuLi (1.6M, 14.6 mL, 23 mmol) was added. The reaction mixture was stirred at –20 °C for 1h, then placed in the freezer at –20°C for 20 h. The mixture was cooled to –40 °C, and a solution of bis(2-fluorophenyl)disulfide (4. 0 g, 15.7 mmoles) in 30 mL THF was added. The reaction mixture was stirred at –35 °C for 3 h. The reaction mixture was poured into 0.5 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to an oil. Purification by sgc (3 % EtOAc / hexanes) gave 1.55 g (62 %) of Compound 29 as a solid..



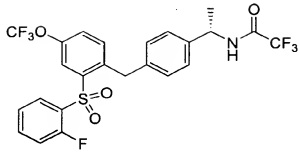
Compound 30

Compound 30. Methyllithium (3.25 mL, 5 mmol, 1.4 M ether) was added to a solution of Compound 1 (1.22 g, 4 mmol) at –70°C. After 10 min n-BuLi (1.6 M in hexanes, 2.83 mL, 5 mmol) was added and stirred for 30 min. A solution of Compound 29 (1.44g, 4.55mmoles), dissolved in THF (15mL) was added. The resulting mixture was stirred at –70 °C for 2.5 h, quenched with water, warmed to 0 °C and then extracted with 2 X 50 mL EtOAc. The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated to an oil. Purification by sgc (EtOAc : hexanes) gave Compound 30 (1.4 g, 58%) as a gum.



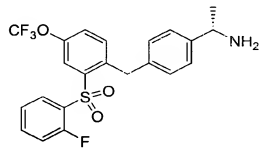
Compound 31

Compound 31. Triethylsilane (3.5 mL, 22.5 mmol) was added to a solution of Compound 30 (0.6 g ,1.125 mmol) in CH_2Cl_2 (30 mL), followed by addition of boron trifluoride etherate (0.32 mL, 1.94 mmol). After stirring at rt for 15 min the reaction mixture was diluted with 50 mL CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and concentrated to give a solid. Purification via PTLC (25%EtOAc/hexanes (1:3) gave Compound 31 (0.47 g, 89 %) as a solid.



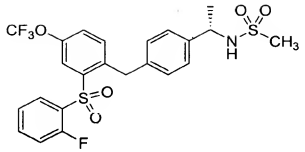
Compound 32

Compound 32. MCPBA (1.56 g (56%), 5.09 mmol) was added to a solution of Compound 31 (0.47 g, 0.9 mmol) in CH_2Cl_2 (30 mL) at rt. After stirring for 16 h the reaction was washed with 5% aq $NaHSO_3$, aq $NaHCO_3$, and water. The organics were dried over Na_2SO_4, filtered, and concentrated to give Compound 31 (0.4 g, 82%) as a solid.



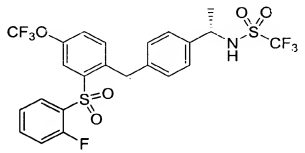
Compound 33

Compound 33. 1 M aq LiOH (9.7 mL, 9.7 mmol) was added to a solution of Compound 32 (1.78 g, 3.2 mmol) in 1,4-dioxane (15 mL). The resulting mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in 50 mL CH_2Cl_2 and washed with 10 mL brine. The organics were dried over Na_2SO_4, filtered and concentrated to an oil, which was used in the next step without additional purification.



Compound 34

Compound 34. Triethylamine (0.28 mL, 2 mmol) was added to a solution of Compound 33 (0.18 g, 0.4 mmol) in CH_2Cl_2 at rt, followed by addition of MsCl (0.061 mL, 7.9 mmol) in 0.2 mL CH_2Cl_2. The mixture was stirred overnight, then washed with 2 X 10 mL water, dried over Na_2SO_4, filtered, and concentrated to give an oil. The oil was purified via PTLC using EtOAc : hexanes (1:1) as the solvent to give Compound 34 (0.137g, 65%) as a solid.

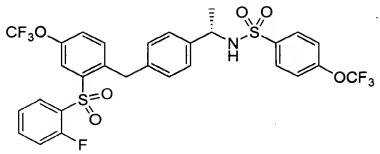


Compound XIX

Compound XIX. Triethylamine (0.296 mL, 2.1 mmol) was added to a solution of Compound 33 (0.4 g, 0.9 mmol) in 8 mL ofCH_2Cl_2, cooled to 0°C, followed by addition of a solution of trifluoromethanesulfonic anhydride (0. 54 g, 1.9 mmol) in CH_2Cl_2 (5 mL) . The mixture was stirred at 0 °C for 3 h, washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give crude Compound XIX. The crude product was purified via PTLC using 33% EtOAc:hexanes to give Compound XIX as a solid (0.32 g, 62%).

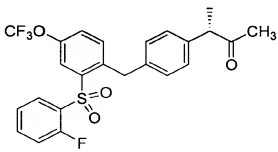
EXAMPLE XIV

Preparation of Sch 445578, Sch 445579, and Sch 446122



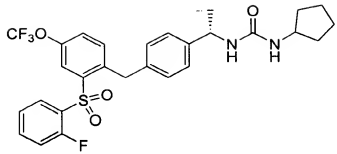
Compound XX

Compound XX. Triethylamine (0.018 mL, 0.129 mmol) was added to a solution of Compound 33 (0.05 g, 0.11 mmol) in CH_2Cl_2 (1.5 mL) followed by addition of 4-(trifluoromethoxy)benzenesulfonyl chloride (0.02 mL, 0.118 mmol) in CH_2Cl_2 at rt. The stirring was continued for 10 h. The reaction mixture was diluted with 50 mL CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by PTLC (33%EtOAc: hexanes to give Compound XX as a solid (0.048 g, 65%).



Compound XXI

Compound XXI. Triethylamine (0.012 mL, 0.086 mmol) was added to a solution of Compound 33 (0.033 g, 0.073 mmol) in CH_2Cl_2 (1 mL) at –5 °C. A solution of acetyl chloride (0.0057 mL, 0.08 mmol) in 0.5 mL CH_2Cl_2 was added. The mixture was stirred overnight at rt. The organics were washed with water, and then dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The resulting crude was purified by PTLC (EtOAc) to provide Compound XXI as a solid (0.009 g, 25%).

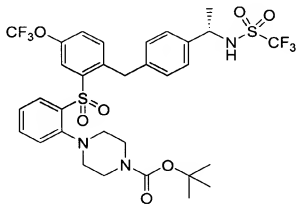


Compound XXII

Compound XXII. Cyclopentyl isocyanate (0.0135 g, 0.12 mmol) was added as a CH_2Cl_2 solution (0.5 mL) to a solution of Compound 33 (0.05 g, 0.11 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the crude product was subjected to PTLC (EtOAc/hexanes 1:2) to provide Compound XXII (0.04 g, 65%).

EXAMPLE XV

Preparation of Sch 479395

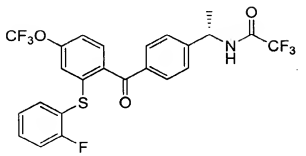


Compound XXIII

Compound XXIII. N-Boc-piperazine (0.5 g, 2.68 mmol) was added to a solution of Compound XIX (0.2 g, 0.34 mmol) in CH_3CN (10 mL). The reaction was heated at 80°C for 72 h. Additional N-Boc-piperazine (0.25 g, 1.34 mmol) was added and heated at 80 °C for another 16 h. The solvent was removed under reduced pressure and the crude product was purified via PTLC (50%EtOAc:hexanes) to provide Compound XXIII as a solid, (0.096 g, 37%).

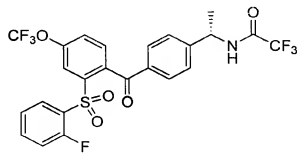
EXAMPLE XVI

Preparation of Sch 418027 and Sch 441847



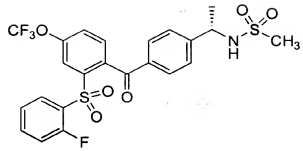
Compound 35

Compound 35. Pyridinium chlorochromate (0.194 g, 0.899 mmol) was added to a mixture of Compound 30 (0.4 g, 0.75 mmol) and Celite (0.4 g) in CH_2Cl_2 (10 mL) at rt. The mixture was stirred for 18 h, filtered through Celite and concentrated. The crude material was purified via PTLC using 33% EtOAc:hexanes to obtain Compound 35 (0.4 g, 100%).



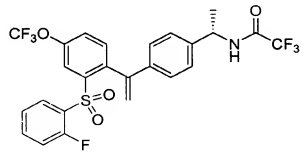
Compound 36

Compound 36. MCPBA (1.29 g (56%), 4.18 mmol) was added to a solution of Compound 35 (0.4 g, 0.75 mmol) in CH_2Cl_2 (20 mL) and stirred at rt for 18 h. The reaction was washed with 5% aq $NaHSO_3$, 5% $NaHCO_3$, and water. The organics were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via PTLC using EtOAc:hexanes (1:1) to provide Compound 36 (0.34 g, 80%).



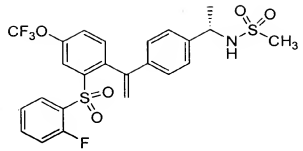
Compound 37

Compound 37. Compound 36 was converted to Compound 37 using a procedure similar to that described in example II.



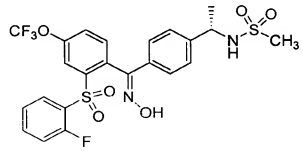
Compound 38

Compound 38. LHMDS (0.9 mL, 1M solution THF, 0.896 mmol) was added to a suspension of methyltriphenylphosphonium bromide (0.215 g, 0.6 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min, then for 10 minutes at rt. A solution of Compound 36 (0.17 g, 0.3 mmol) in THF (8mL) was added and stirring continued for 10 h at rt. The mixture was diluted with EtOAc and washed with water. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified via PTLC using EtOAc:hexanes (1:3) to provide Compound 38 as a solid. (0.09 g, 54%).



Compound XXIV

Compound XXIV. Compound 38 was converted to Compound XXIV using a procedure similar to that described in example II.

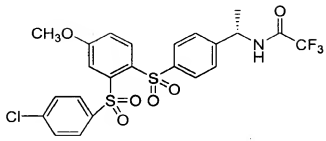


Compound XXV

Compound XXV. Hydroxylamine hydrochloride (0.076 g, 1.09 mmol) was added to a solution of Compound 37 (0.03 g, 0.055 mmol) in pyridine (0.5 mL). The mixture was heated at 80 °C for 24 h. The mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL CH_2Cl_2 and washed with water and brine. The organics were dried over Na_2SO_4, filtered and concentrated to provide crude Compound XXV, which was purified via PTLC (EtOAc/hexanes, 1:3) to afford Compound XXV as a solid (0.01 g, 33%).

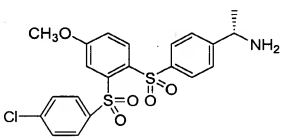
EXAMPLE XVII

Preparation of Sch 355365



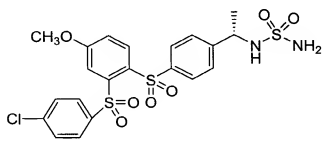
Compound 39

Compound 39. In a flame dried flask under N_2 blanket, Compound 2 (4.00 g, 10.32 mmol) was dissolved in anhyd THF (41 mL) and cooled to –78°C. A solution of n-BuLi (2.5 M in hexanes, 8.25 mL, 20.6 mmol) was added and the reaction mixture was stirred for 25 min. Bis-4-chlorophenyl disulfide (3.10 g/ 10.8 mmol) was added and the reaction mixture was stirred at –78°C for 3 h then between –78 °C and -10°C for 3 h. The reaction mixture was quenched with pH 7.0 sodium phosphate buffer (1.0 M, 50 mL). The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, then dried with Na_2SO_4 and concentrated to dryness. The crude product (5.44 g foam) was dissolved in CH_2Cl_2 (120 mL) and cooled to 0°C. MCPBA (7.24 g) was added. The ice bath was removed and the reaction mixture was stirred at rt overnight. Aqueous $NaHCO_3$ and CH_2Cl_2 were added and the layers were separated. The organic layer was washed with aq $NaHSO_3$, $NaHCO_3$, H_2O, and brine then dried with $MgSO_4$. The crude product was purified by sgc (35%-40% EtOAc/hexanes gradient) to give 1.86 g (32%) of Compound 39.



Compound 40

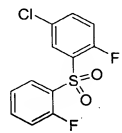
Compound 40. Compound 39 (1.52 g, 2.70 mmol) was dissolved in dioxane (9 mL) and cooled to 0°C. LiOH (1.0 M aq, 3 mL, 3 mmol) was added and the reaction mixture was left stirring overnight, during which time it warmed to rt. The solvents were evaporated. CH_2Cl_2 and aq NaOH were added and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with Na_2SO_4 and concentrated to give 0.85 g (68%) of Compound 40.



Compound XXVI

Compound XXVI. Compound 40 (143 mg, 0.307 mmol) was dissolved in dioxane and sulfamide (0.128, 1.33 mmol) was added. The reaction mixture was stirred at reflux for 24 h then allowed to cool to rt and concentrated. The reaction mixture was purified via PTLC (5% MeOH/CH_2Cl_2) giving 54 mg (32%) of Compound XXVI.

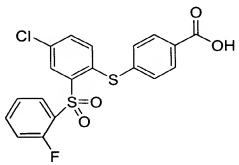
Example XVIII



Compound 41

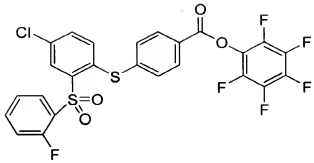
Compound 41. In a flame dried flask under N_2 blanket, 1-chloro-4-fluorobenzene (7.36 g, 56.4 mmol) was dissolved in anhyd THF and cooled in a dry ice/acetone bath. n-BuLi (2.5 M in hexanes, 22.5 mL, 56.3 mmol) was added and the

reaction was stirred for 50 min. 2-Fluorobenzene sulfonyl fluoride (10.3 g, 57.8 mmol) was added and the reaction mixture was left stirring overnight, during which time it warmed to rt. Saturated aq NH_4Cl (100 mL) was added, followed by EtOAc (100 mL) and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. The solvents were evaporated and the crude product was purified via sgc (10% EtOAc/hexanes) to afford Compound 41 (2.55 g, 16%) as a solid.



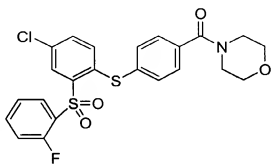
Compound 42

Compound 42. 4-Mercaptobenzoic acid (0.54 g, 3.50 mmol) was dissolved in DMA (10 mL) and cooled in an ice bath. Sodium hydride (60% suspension in oil, 0.30 g, 7.5 mmol) was added and the reaction mixture was stirred for 20 min. The ice bath was removed and the reaction mixture was stirred for 1 h. The flask was cooled to 0°C again and compound 41 (1.0 g, 3.46 mmol) dissolved in DMA (5 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to rt and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aq HCl, water, and brine. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified via sgc (5% MeOH/CH_2Cl_2) to give Coompound 42 as a solid (1.04 g, 71%).



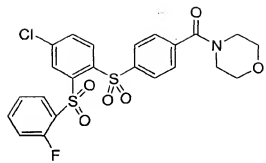
Compound 43

Compound 43. Pentafluorophenol (0.91 g, 4.94 mmol) and Compound 42 (1.04 g, 2.46 mmol) were dissolved in 30 mL of CH_2Cl_2 and EDCI was added. The reaction was stirred overnight and diluted with water and CH_2Cl_2. The layers were separated and the organic layer was washed with water and dried with Na_2SO_4. The crude product was purified via sgc (5% EtOAc/hexanes) to give 0.9 g (62%) of Compound 43 as a solid.



Compound XXVII

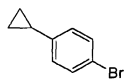
Compound XXVII. Compound 43 (0.15 g, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL). Morpholine (44 mg, 0.51 mmol) and DIPEA (49 mg, 0.38 mmol) were added and the reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with EtOAc and washed with 5% aq $NaHCO_3$, water and brine. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified via sgc (50% EtOAc/hexanes) to give 98 mg (77%) of Compound XXVII.



Compound XXVIII

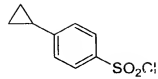
Compound XXVIII. Compound XXXVII (72 mg, 0.146 mmol) was dissolved in CH_2Cl_2 (3 mL) and MCPBA (ca 50%, 0.11 g, ca 0.36 mmol) was added. The reaction mixture was stirred overnight then diluted with CH_2Cl_2. The reaction mixture was washed with aq Na_2CO_3 and water then dried with Na_2SO_4. The solvents were evaporated and the crude product was purified via sgc (60% EtOAc/hexanes) to give 61 mg (79%) of Compound XXXVIII as a solid.

Example XIX



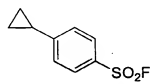
Compound 44

Compound 44. Cyclopropyl benzene (48.5 g, 410 mmol), glacial acetic acid (510 mL), and sodium acetate (38.9 g, 474 mmol) were added to a roundbottomed flask. The flask was cooled in an ice-water bath. A solution of bromine (66.3 g, 414 mmol) dissolved in 105 mL of acetic acid was added dropwise over 90 min. The reaction mixture was stirred at temperatures between 0 °C and 10 °C for 5 h. The reaction was then allowed to warm to rt overnight. Hexanes (1300 mL) and water (250 mL) were added. Aqueous $NaHSO_3$ (1M) was added until the reaction mixture changed from yellow to clear. The layers were separated. The organic layer was washed with water, 1M aq Na_2CO_3, and brine, then dried with Na_2SO_4. The solvent was evaporated and the crude product was purified *via* sgc using hexanes as the mobile phase to give 17 g of p-cyclopropylbromobenzene (21%) (Compound 44).



Compound 45

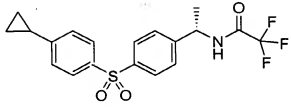
Compound 45. A flask was flame dried under N_2 blanket. Compound 44 (10.0 g, 50.7 mmol) was added, followed by dry THF (100 mL). The resulting solution was cooled to –78 °C. A solution of n-butyl lithium in hexanes (2.27 M, 22.35 mL, 50.7 mmol) was added dropwise *via* syringe. The reaction mixture was stirred for 10 min. SO_2 gas was bubbled into the reaction mixture until the pH of a reaction mixture sample was <1 when mixed with water. The reaction mixture was stirred for 30 min at –78 °C. The ice bath was removed and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred for an additional 30 min at rt. The reaction mixture was concentrated to afford a solid. CH_2Cl_2 (500 mL) and N-chlorosuccinamide (10.2 g, 76 mmol) were added and the reaction mixture was stirred for 4 hrs at rt. Water and CH_2Cl_2 were added and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. The solution was filtered and the solvents were evaporated to give 13.3 g of crude p-cyclopropyl-benzenesulfonyl chloride (Compound 45).



Compound 46

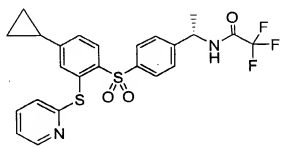
Compound 46. Crude compound 45 (13.3 g) was dissolved in 200 mL of acetone and 60 mL of water. Potassium fluoride (7.12 g, 122 mmol) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na_2SO_4, filtered, and

concentrated to dryness to give 9.80 g (97%) of crude p-cyclopropyl benzenesulfonyl fluoride (Compound 46).



Compound 47

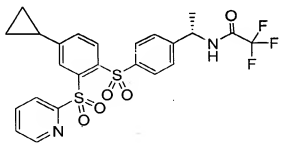
Compound 47. A flask was flame dried under N_2 blanket. Compound 1 (44.29 g, 150 mmol) was added, followed by 500 mL of anhydrous THF. The flask was cooled to –78 °C and a solution of n-butyl lithium in hexanes (1.77 M, 154 mL, 272 mmol) was added over 40 min. The reaction mixture was stirred for 1.5 h at –78 °C, then transferred *via* cannula into a solution of crude p-cyclopropylbenzenesulfonyl fluoride (27.2 g, 135 mmol) dissolved in 200 mL of anhydrous THF over 1.5 h. The reaction mixture was stirred for 1h. Water was added, followed by EtOAc. The layers were separated and the organic layer was washed with aq NH_4Cl, water, and brine, then dried with Na_2SO_4. The solvents were evaporated, and the crude product was purified by sgc (25%-33% EtOAc/Hexanes gradient mobile phase) to give 24.5 g (45%) of compound 47.



Compound 48

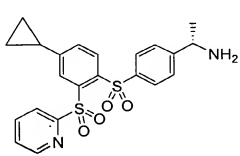
Compound 48. A flask was flame dried under N_2 blanket. Compound 47 (16.33 g, 41.1 mmol) was dissolved in 400 mL of anhydrous THF and cooled to –78

°C. A solution of n-butyl lithium in hexanes (2.3 M, 35.7 mL, 82.1 mmol) was added dropwise *via* syringe. The reaction mixture was stirred for 1.5 h at –78 °C. A solution of 2, 2'-dithiodipyridine (8.89 g, 41.1 mmol) dissolved in 40 mL of THF was added and the reaction mixture was stirred for 2 h. The cold bath was removed, and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was cooled with an ice-water bath and the reaction was quenched with 10 mL of water. The reaction mixture was diluted with EtOAc and washed with saturated aq NH_4Cl, water, and brine. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified via sgc using 1:2 EtOAc/Hexanes as the mobile phase giving 15.49 g (74%) of Compound 48.



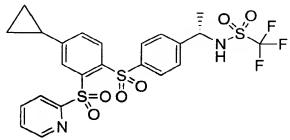
Compound 49

Compound 49. Compound 48 (15.49 g, 30.6 mmol) was dissolved in 1 L of CH_2Cl_2 and the flask was placed in a rt water bath. MCPBA (22.0 g, *ca* 74 mmol) was added in portions and the reaction mixture was left stirring overnight at rt. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% aq $NaHCO_3$, water, and brine, then dried with Na_2SO_4. The solvent was evaporated and the crude product was purified *via* sgc using a 20%-50% EtOAc/Hexanes gradient as the mobile phase. Compound 49 (9.4 g, 57%) was isolated as a solid.



Compound 50

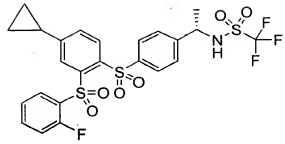
Compound 50. Compound 49 (10.16 g, 18.87 mmol) was dissolved in 300 mL of p-dioxane and 300 mL of 1.0 M aq LiOH was added. The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with CH_2Cl_2. The layers were separated, and the organic layer was washed with water and brine, then dried with Na_2SO_4. The solvents were evaporated to give 9.0 g of crude Compound 50.



Compound XXIX

Compound XXIX. Crude compound 50 (7.74 g, 17.5 mmol) was dissolved in CH_2Cl_2 (250 mL). Diisopropylethylamine (2.71 g, 21 mmol) was added and the flask was cooled to –78 °C. A solution of triflic anhydride (5.97 g, 21.1 mmol) dissolved in CH_2Cl_2 (50mL) was added dropwise over 1h. The reaction mixture was stirred for 2 h at –78 °C. The cold bath was removed, and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified *via* sgc using 1:2 EtOAc/Hexanes as the mobile phase to give 8.61 g (85%) of Compound XXIX.

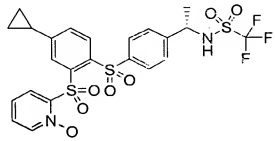
Compound XXIX: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56-8.52 (m, 1H), 8.32-8.21 (m, 3H), 8.02-7.92 (m, 4H), 5.42 (d, 9 Hz, 1H), 8.02-7.92 (m, 4H), 5.42 (d, 1H, 9 Hz), 4.84-4.78 (m, 1H), 2.16-2.06 (m, 1H), 1.60 (d, 7Hz, 3H), 1.20-1.17 (m, 2H), 0.97-0.89 (m, 1H).



Compound XXX

Compound XXX. Compound XXX was prepared from compound 47 using the procedures in example II.

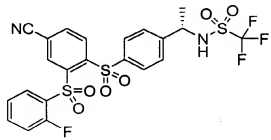
Compound XXX: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33-8.22 (m, 3H), 8.00-7.94 (m, 2H), 7.66-7.58 (m, 1H), 7.53-7.37 (m, 4H), 7.16-7.05 (m, 1H), 5.160 (d, 9 Hz, 1H), 4.88-4.83 (m, 1H), 2.17-2.06 (m, 1H), 1.65 (d, 7 Hz, 3H), 1.28-1.20 (m, 2H), 0.97-0.90 (m, 2H).



Compound XXXI

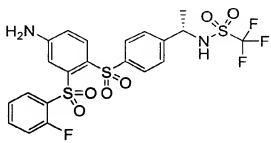
Compound XXXI. The potassium salt of compound XXIX (56 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (5 mL) and Na_2HPO_4 (0.13 g, 0.91 mmol), and urea-hydrogen peroxide complex (85 mg, 0.90 mmol) were added. Trifluoroacetic acid was added (47 mg, 0.22 mmol) and the reaction mixture was refluxed for 4 h then left stirring overnight at rt. Additional urea-hydrogen peroxide complex (85 mg, 0.9 mmol) and TFAA (0.56 mmol) were added and the reaction mixture was refluxed for 6h. The reaction mixture was allowed to cool to rt and diluted with CH_2Cl_2 and water. The layers were separated and the organic layer was washed with water, dried with Na_2SO_4, and concentrated. The crude product was purified *via* PTLC on silica using EtOAc as the mobile phase to give 34 mg (64%) of compound XXXI.

Compound XXXI: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38-8.29 (m, 2H), 8.17 (d, 8 Hz, 1H), 8.07-8.02 (m, 1H), 7.91-7.85 (m, 2H), 7.56-7.36 (m, 5H), 6.11 (d, 8 Hz, 1H), 4.84-4.78 (m, 1H), 2.12-2.01 (m, 1H), 1.57 (d, 7Hz, 3H), 1.21-1.12 (m, 2H), 0.92-0.86 (m, 2H).



Compound XXXII

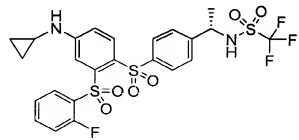
Compound XXXII. Compound V (0.50 g, 0.85 mmol), zinc (II) cyanide (65 mg, 0.55 mmol), zinc dust (11 mg, 0.17 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (21 mg, 0.04 mmol), and tris(dibenzylidineacetone) dipalladium (17 mg, 0.129 mmol) were added to a 25 mL flask. Dimethylacetamide was added and the reaction mixture was placed under N_2 blanket and heated to 110 °C. The reaction mixture was stirred at 110 °C for 4 h, then partitioned between EtOAc and water. The organic layer was washed with 2M ammonium hydroxide, water, and brine, then dried with $MgSO_4$. Evaporation of the solvent afforded 0.49 g of an oil that was purified *via* sgc using a 20%-25% EtOAc/Hexanes gradient mobile phase to afford compound XXXII (0.20 g).



Compound XXXIII

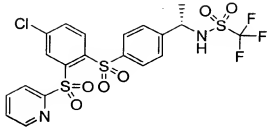
Compound XXXIII. Compound V (0.51 g, 0.87 mmol), tris(dibenzylidineacetone) dipalladium (40 mg, 0.04 mmol), 2-(dicyclohexylphosphino)-

biphenyl (36 mg, 0.103 mmol), and sodium tert-butoxide (204 mg, 2.12 mmol) were added to a Schlenck flask under N_2 blanket. Toluene (2.5 mL) was added, followed by benzophenone imine (210 mg, 1.15 mmol). The reaction mixture was stirred overnight at 70 °C under N_2. The reaction mixture was allowed to cool to rt and 1 M aq HCl was added. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. The resulting material was filtered and concentrated to give 0.37 g of an oil. The crude product was purified *via* sgc using a 25%-50% EtOAc/Hexanes gradient mobile phase, followed by a 5%MeOH/45%EtOAc/50%Hexanes mobile phase to give 0.11 g of an oil as product.



Compound XXXIV

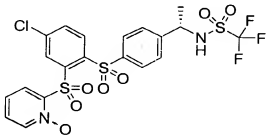
Compound XXXIV. Compound V (264 mg, 0.45 mmol), sodium tert-butoxide (103 mg, 1.07 mmol), tris(dibenzylideneacetone) dipalladium (107 mg, 0.116 mmol), and 2-(di-tert-butyl-phosphino)biphenyl (61 mg, 0.20 mmol) were added to a Schlenck flask under N_2. THF (1.5 mL) and cyclopropylamine (0.6 g, 10.5 mmol) were added and the reaction mixture was stirred for 24 h at rt. EtOAc and 1 M aq HCl were added and the layers were separated. The organic layer was washed with 1 M aq HCl, water, and brine, then dried with $MgSO_4$. Filtration and evaporation of the solvents gave an oil which was purified *via* sgc using 25% EtOAc/Hexanes as the mobile phase. Compound XXIV (109 mg) was obtained as a foam.



Compound XXXV

Compound XXXV. Compound XXXV was prepared from compound 5 according to the procedures in Example XIX.

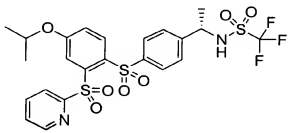
Compound XXXV: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (d, 1.2 Hz, 1H), 8.51-8.56 (m, 2H), 8.31 (dd, 8 Hz, 1 Hz, 1H), 8.18 (dd, 8 Hz, 1 Hz, 1H), 8.08-7.96 (m, 3H), 7.62-7.48 (m, 3H), 5.51 (d, 9Hz, 1H), 4.90-4.70 (m, 1H), 1.62 (d, 7 Hz, 3H).



Compound XXXVI

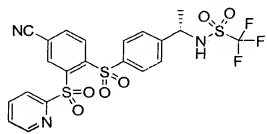
Compound XXXVI. Compound XXXVI was prepared from compound XXXV according to the procedure in Example XIX.

Compound XXXVI: ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (d, 7.8 Hz, 1H), 8.27-8.42 (m, 4H), 8.13 (dd, 7.8 Hz, 2.1 Hz, 1H), 7.93 (d, 8.4 Hz, 2H), 7.78-7.63 (m, 2H), 7.59 (d, 8.4 Hz, 2H), 4.80 (m, 1H), 1.44 (d, 6.9 Hz, 3H).



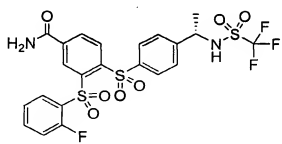
Compound XXXVII

Compound XXXVII. Compound XXXV (0.312 g, 0.548 mmol) was dissolved in 2 propanol (20 mL) and 1.0 M aq NaOH was added (10 mL). The reaction mixture was stirred at temperatures between 80 °C to 84 °C for six days. The reaction mixture was allowed to cool to rt and partially concentrated. EtOAc was added and the layers were separated. The aqueous layer was acidified with 1 M aq H_2SO_4 and extracted with EtOAc. The combined organic layer was dried with $MgSO_4$ and concentrated to give 0.29 g of an oil. The crude product was purified via sgc using a 25%-33% EtOAc/Hexanes gradient as the mobile phase. The fraction containing Compound XXVII was repurified via sgc using 3% MeOH/CH_2Cl_2 as the mobile phase to give 0.05 g (15%) of Compound XXXVII as a solid.



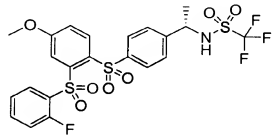
Compound XXXVIII

Compound XXXVIII. Compound XXXVIII was prepared from compound XXXV according to the procedure used to prepare compound XXXII.



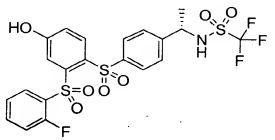
Compound XXXIX

Compound XXXIX. Compound XXXII (0.10 g, 0.17 mmol) was dissolved in acetone (1.5 mL) and water (1 mL). Potassium carbonate (3 mg, 0.022 mmol) and urea-hydrogen peroxide complex (0.16 g, 1.70 mmol) were added and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with water. The solvents were evaporated and the crude product was purified via PTLC on SiO_2 using 50% EtOAc/Hexanes as the mobile phase to afford Compound XXXIX (75 mg, 73%) as a solid.



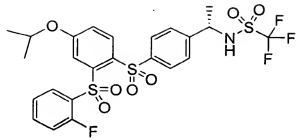
Compound XXXX

Compound XXXX. Compound XXXX was prepared from compound 2 according to the procedures in Example II.



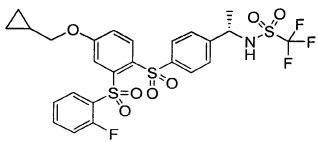
Compound XXXXI

Compound XXXXI. Compound XXXXI was prepared from compound XXXX according to the procedure used to convert compound 16 to compound X.



Compound XXXXII

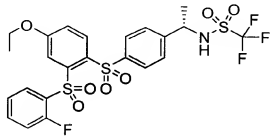
Compound XXXXII. Compound XXXXI (0.15 g, 0.264 mmol) was dissolved in DMA (5 mL). Potassium iodide (0.22 g, 1.30 mmol), cesium carbonate (0.19 g, 0.58 mmol), and 2-bromopropane (49 mg, 0.398 mmol) were added and the reaction mixture was left stirring at rt over the weekend. EtOAc was added and the reaction mixture was washed with satd. aq NH_4Cl and water. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified *via* sgc using 3% Et_2O/CH_2Cl_2 as the mobile phase to give 83 mg (51%) of Compound XXXXIi.



Compound XXXXIII

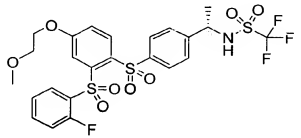
Compound XXXXIII. Compound XXXXI (0.10 g, 0.176 mmol) was dissolved in DMF (2 mL). Sodium hydride (7 mg, *ca* 1.2 eq) and bromomethylcyclopropane (26 mg, 0.19 mmol) were added and the reaction was stirred at 50 °C for 4 hr then allowed to cool to rt. EtOAc and water were added, and the layers were separated. The organic layer was washed with water and dried with Na_2SO_4. The solvent was

evaporated and the crude product was purified via sgc using 33% EtOAc/Hexanes as the mobile phase to give 15 mg (14%) of Compound XXXXIII.



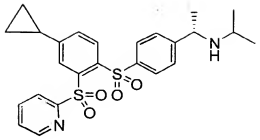
Compound XXXXIV

Compound XXXXIV. Compound XXXXIV was prepared according to the procedure used for Compound XXXXIII using ethyl iodide as the electrophile and stirring the reaction at rt overnight before workup.



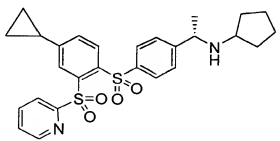
Compound XXXXV

Compound XXXXV. Compound XXXXI (0.40 g, 0.70 mmol) was dissolved in DMF (8 mL) and NaH (62 mg, ca 2.2 eq) was added. The reaction mixture was stirred for 30 min. Sodium iodide (0.52 g, 3.46 mmol) and 2-chloroethyl methyl ether (80 mg, 0.85 mmol) were added. The reaction mixture was stirred for 1 h at rt then 5 h at 110 °C. The reaction mixture was allowed to cool to rt. EtOAc and satd aq NH_4Cl were added and the layers were separated. The organic layer was washed with water and dried with Na_2SO_4. Evaporation of the solvent, followed by sgc using 50% EtOAc/Hexanes as the mobile phase, afforded 0.21 g (48%) of Compound XXXXV.



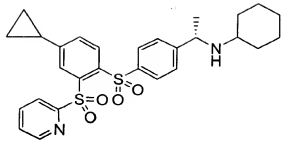
Compound XXXXVI

Compound XXXXVI. Compound 50 (50 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (3 mL) and acetic acid (7 mg). Acetone (6 mg, 0.13 mmol), and $NaBH(OAc)_3$ (36 mg, 0.169) were added, and the reaction mixture was left stirring at rt overnight. EtOAc was added and the reaction mixture was washed with 10% Na_2CO_3 and water. The solvents were evaporated and the crude product was purified via PTLC on SiO_2 using EtOAc as the mobile phase. The resulting product was dissolved in EtOAc and HCl in Et_2O was added causing a white precipitate to form. The solvent was removed and the precipitate was washed with Et_2O and dried *in vacuo* to give 32 mg (49%) of compound XXXXVI as a solid.



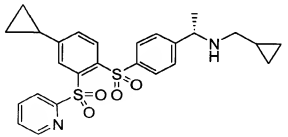
Compound XXXXVII

Compound XXXXVII. Compound XXXXVII was prepared according to the procedure used for compound XXXXVI using cyclopentanone as the carbonyl source.



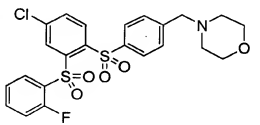
Compound XXXXVIII

Compound XXXXVIII. Compound XXXXVIII was prepared according to the procedure used for compound XXXXVI using cyclohexanone as the carbonyl source.



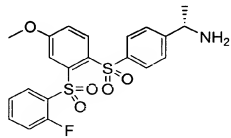
Compound XXXXIX

Compound XXXXIX. Compound XXXXIX was prepared according to the procedure used for compound XXXXVI using cyclopropanecarboxaldehyde as the carbonyl source.



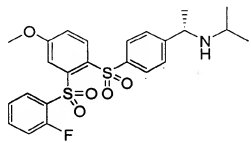
Compound L

Compound L. Compound XXVIII (0.10 g, 0.197 mmol) was dissolved in a solution of borane in THF (1.0 M, 1.0 mL, 1.0 mmol). The reaction mixture was refluxed for 4 h then allowed to cool to rt. The solution was concentrated. Methanol (5 mL) and 1 M aq HCl (5 mL) were added and the resulting solution was stirred for 5 h at rt. The reaction mixture was concentrated and EtOAc was added. The resulting solution was washed with aq NaOH and water, then dried with Na_2SO_4. The solvent was evaporated and the crude product was purified via PTLC using 40% EtOAc/Hexanes as the mobile phase. The product isolated from this step was dissolved in EtOAC, and HCl in Et_2O was added causing a precipitate to form. The solvent was removed and the precipitate was washed with Et_2O and dried *in vacuo* to give 22 mg (21%) of Compound L as a solid.



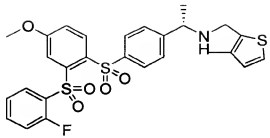
Compound 51

Compound 51 was prepared from Compound 2 according to the procedures in Example 11.



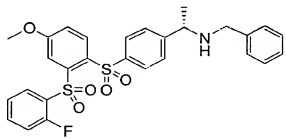
Compound LI

Compound LI. Compound LI was prepared from compound 51 according to the procedure used to prepare compound XXXXVI.



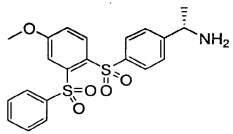
Compound LII

Compound LII. Compound LII was prepared from compound 51 according to the procedure used to prepare compound XXXXVI using 3-methyl-2-thiophenecarboxaldehyde as the carbonyl source.



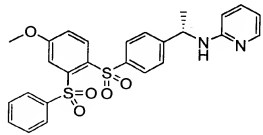
Compound LIII

Compound LIII. Compound LIII was prepared from compound 51 according to the procedure used to prepare compound XXXXVI using benzaldehyde as the carbonyl source.



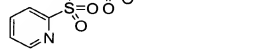
Compound 52

Compound 52. Compound 52 was prepared from compound 2 using the procedures in Example II with benzenesulfonyl fluoride as the initial electrophile.



Compound LIV

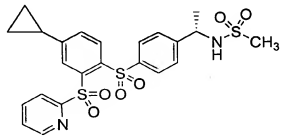
Compound LIV. Compound 52 (0.29 g, 0.67 mmol), cesium carbonate (0.44 g, 1.35 mmol), tris(dibenzylideneacetone) dipalladium (31 mg, 0.034 mmol), dppp (28 mg, 0.068 mmol), and 2-bromopyridine (0.16 g, 1.01 mmol) were dissolved in 11 mL of toluene under N_2 blanket. The reaction mixture was stirred at 80 °C overnight under N_2, then allowed to cool to rt. CH_2Cl_2 was added and the reaction mixture was washed with 2M aq $NaHCO_3$, water, and brine. The organic layer was dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified *via* sgc using EtOAc as the mobile phase. The resulting material was dissolved in EtOAc and a solution of HCl/Et_2O was added. The solvents were evaporated to give 145 mg (42%) of Compound LIV as a solid.



Compound LV

Compound LV. Compound XXXV (0.92 g, 1.67 mmol), was dissolved in methanol (40 mL) and 1.0 M aq NaOH was added (20 mL). The reaction mixture was stirred at 70 °C for 21 h. The reaction mixture was concentrated and extracted with EtOAc. The organic layer was washed with 1 M aq HCl, water, and brine, then dried with $MgSO_4$. The solvent was evaporated and the crude product was purified via sgc using 25%-33% EtOAc/Hexanes as the mobile phase. Compound LV (0.82 g, 90%) was isolated as an oil.

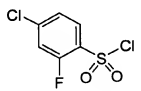
Compound XXXXV: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, 3.9 Hz, 1H), 8.31-8.22 (m, 2H), 8.124 (d, 2.7 Hz, 1H), 8.05-7.95 (m, 1H), 7.92 (d, 8.4 Hz, 2H), .750-7.45 (m, 1H), 7.92 (d, 8.4 Hz, 2H), 7.27-7.23 (m, 2H), 5.8 (d, NH, 1H), 4.85-4.75 (m, 1H), 3.99 (s, 3H), 1.58 (d, 7.2 Hz, 3H).



Compound LVI

Compound LVI. Compound 50 was converted to compound LVI according to the procedure in Example II.

Compound LVI: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56-8.52 (m, 1H), 8.31-8.23 (m, 3H), 8.02-7.90 (M, 4H), 4.87-4.78 (d, 7 Hz, 1H), 4.69 (m, 1 H), 2.66 (s, 3H), 2.16-2.06 (m, 1H), 1.51 (d, 7 Hz, 3H), 1.27 –1.17 (m, 2H), 0.96-0.90 (m, 2H).



Compound 53

Compound 53. 2-fluoro-4-chloroaniline (22.90 g, 151 mmol) was dissolved in 120 mL of AcOH and 80 mL of concentrated HCl was added with stirring. The